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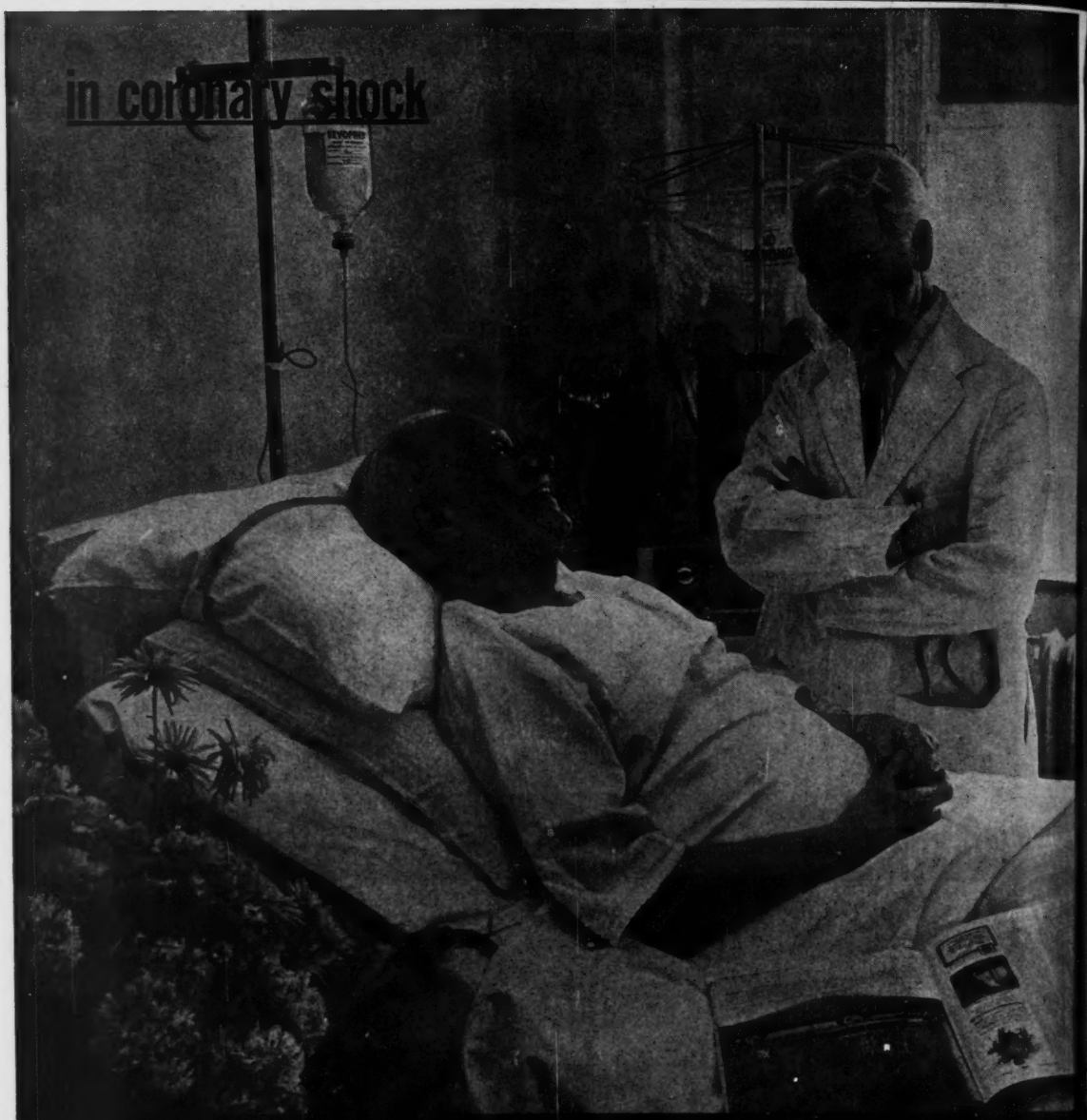

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Editorial

Long-Term Electric Pacemakers for Stokes-Adams Disease

THE MAJOR problem in Stokes-Adams disease remains the prevention of recurrent seizures. Patients with atrioventricular block now can be resuscitated from ventricular standstill, tachycardia, and fibrillation by the new technics of external electric stimulation and external countershock defibrillation.[1, 2] Despite available pharmacologic measures, however, attacks often recur and may be fatal. For assured prevention of seizures, whether due to ventricular standstill or fibrillation, the unreliable intrinsic ventricular pacemaker must be replaced by a reliable electric one to drive the ventricle continuously and indefinitely.

Because of the desperate nature of these problems in some patients, attempts have already been made by several investigators to provide a permanent electric cardiac pacemaker. We shall consider here the many problems that must be recognized and solved before this approach is widely used.

External Stimulation

External electric stimulation of the heart to arouse ventricular beats is most valuable in emergency resuscitation from ventricular standstill. It has been used continuously for over 2 weeks in patients with no intrinsic ventricular activity, and almost continuously for periods up to 8 months in patients with frequently recurrent Stokes-Adams attacks. Long-term use of this technic is usually impractical, however, because of local pain from stimulation, and because of skin irritation and ulcerations from the electrodes. Intermittent rather than continuous stimulation would reduce the pain, but continuous cardiac monitoring would then be necessary to assure prompt resuscitation; the size of the apparatus would hamper freedom of movement and skin irritation would still occur.

Direct Stimulation

Direct electric stimulation with electrodes on or in the heart obviates the difficulties of long-term external stimulation: pain and skin irritation are eliminated. With a technic of continual long-term direct stimulation we envisage that the ventricles would be driven continuously and indefinitely, regardless of the presence or absence of intrinsic ventricular activity. Continual stimulation would not require monitoring or automatic triggering devices; it would provide an uncomplicated and reliable means of preventing recurrent Stokes-Adams attacks. Complete suppression of an intrinsic ventricular pacemaker by an artificial one or competition between them does not create clinical difficulties: some irregularity of rhythm may occur but is of no clinical import; although the stroke volume of ectopic ventricular beats may be somewhat diminished, adequate circulation can be maintained for long periods by an electric pacemaker.

Direct electric stimulation of the heart does

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carry a risk of ventricular fibrillation that is not present with external stimulation: stimuli applied directly to the heart may produce multiple ventricular responses and ventricular fibrillation.[3] These untoward responses are particularly likely to occur when the stimuli are well above threshold intensity or are longer in duration than the recommended 2 to 3 milliseconds.[4] This phenomenon of multiple responses to a single electric stimulus, however, has not been observed during extensive experimental and clinical experiences with external stimulation.[4] The reason for this difference between direct and external electric stimulation is not clear; it may be related to quantitative differences in the current applied to the heart in these two ways. At present, although the risk of fibrillation does not appear to be great, it cannot be definitively assessed. The technic of direct stimulation should, therefore, be used for appropriate patients but with care and with awareness of its potential hazard.

Direct electric stimulation also carries a risk of ventricular fibrillation from technical accidents. When testing or recording instruments (oscilloscopes, galvanometers, electrocardiographs) are attached to wires leading to the heart, small currents may leak from them and produce ventricular fibrillation. No such apparatus should be attached to wires leading to the heart until all the instruments have been properly grounded and the possible transfer of a small, unrecognized but potentially lethal current has been eliminated. We know of several instances in which transient fibrillation was inadvertently produced in this way.

Weirich et al.[5] introduced a technic of implanting a myocardial electrode for direct cardiac stimulation in patients who developed block after open-heart surgery. The myocardial electrode is connected by a wire traversing the chest wall to a small, portable, battery-powered pacemaker. Stimulation by this technic is painless and is particularly useful in these patients because the heart block is usually transient. Cardiac stimulation by this technic, however, usually becomes ineffective within 8 weeks because of a rising threshold for stimulation, presumably due to tissue reaction around the myocardial electrode. Furthermore, with wires through the skin there are significant risks of infection, trauma to the tissues, breakage, and other accidental loss of electric contact. These limitations make this technic unsatisfactory for the usual patients with chronic atrioventricular block and Stokes-Adams disease in whom long-term stimulation is desired. Nevertheless, thoracotomies have been performed for the application of this technic in several such patients, but it was useful only temporarily.

The problem of the rising threshold, which is the major obstacle to long-term direct cardiac stimulation, is being studied intensively. Hunter has developed a bipolar myocardial electrode of stainless steel imbedded in a silicone plastic (Dow Corning Corp. Silastic S-2200) with which he has been able to stimulate the hearts of dogs and of 1 patient for several months.[6] By now this electrode has been implanted in a number of other patients. We have devised myocardial electrodes of platinum insulated with Teflon with which stimulation has remained effective in the dog for over 8 months at the time of the last testing. If these technics prove successful and safe, then direct long-term electric stimulation of the heart, with all its implications of control of Stokes-Adams disease, will become a feasible technic of great clinical promise.

Direct cardiac stimulation has been accomplished without thoracotomy by introducing a myocardial electrode by blind percutaneous puncture.[7, 8] This approach carries the risks of cardiac puncture, which include hemorrhage and multifocal ventricular activity with fibrillation from the needle, and of infection. It also seems that movement of the wire with consequent sudden loss of effective stimulation would be a likely accident. Furthermore, this technic would seem useful only for short-term purposes, since it does not overcome the problem of the rising threshold for stimulation.

Thoracotomy has also been avoided by introducing a catheter containing a wire into the right ventricular cavity by way of a peripheral

eral or jugular vein.[9] Infection, thrombosis and embolism, cardiac damage, and cardiac arrhythmias are significant hazards that persist as long as the catheter is in place. Stokes-Adams attacks have been prevented by such an endocardial electrode for as long as 3 months in 1 patient. It would seem, however, that the use of a myocardial electrode, even though it involves thoracotomy, would be less hazardous and therefore preferable for long-term cardiac stimulation. At the present time, if external stimulation should prove intolerable, for short-term purposes we would probably choose the technic of percutaneous puncture to stimulate the heart directly, because it seems simpler and less hazardous than the use of an endocardial electrode.

The Rate of Stimulation

Once the problem of direct, long-term electric stimulation is solved, it must be decided at what rate to drive the heart. The usual idioventricular rate of 25 to 45 beats per minute in patients with complete heart block is adequate to prevent seizures and is compatible with normal activity for many years. Functionally, however, such rates are insufficient in that cardiac hypertrophy almost invariably occurs, and limitation of exercise tolerance and congestive failure often develop.[10] It would seem, therefore, that driving the heart at a fixed rate between 70 and 90 beats per minute would provide a greater cardiac output with smaller stroke volume and would more adequately meet increased demands upon the heart, as with exercise.

Recent workers have suggested the desirability of driving the heart at the natural, physiologically variable sinoatrial rate rather than at an arbitrary fixed rate.[11, 12] Following the lead of Butterworth and Poindexter,[13] by artificial electronic means they have used the atrial impulse to stimulate the ventricle. These artificial atrioventricular conducting schemes involved 2 sets of wires through the chest wall and external electronic amplifiers and other devices. In addition, safeguards were perforce included in the systems to prevent ventricular slowing or tachycardia in response to atrial arrhythmias. It would seem, therefore, that the theoretical advantages of a physiologically variable rate over a fixed one are not sufficient to justify the complicated systems necessary at present.

Attempts have also been made to restore atrioventricular conduction by surgical union of atrial and ventricular muscle. Erlanger,[14] in 1909, and others subsequently found that this could not be done in experimental animals and a recent report of 1 clinical trial is unconvincing.[15]

The Pacemaker for Direct Stimulation

Since the current necessary to stimulate the heart directly is relatively small, suitable pacemakers have been made that are easily portable, being battery-powered and pocket-sized. In all the methods for direct stimulation that we have discussed, the pacemakers have been attached to the cardiac electrodes by wires traversing the skin, which introduced the risks of infection and trauma. For the patient with Stokes-Adams disease in whom we envisage life-long, continuous stimulation, once the problem of the rising threshold and the safety of direct stimulation are settled, this objectionable feature must be eliminated.

We have developed a small, transistorized, battery-powered pulse generator and radiofrequency transmitter that transmits a signal through the skin to a small subcutaneous receiver (a transistorized diode detector) from which wires deliver the stimulus to the heart. The feasibility of this technic was demonstrated by us experimentally,[16] and since then a similar device was used by others for a short period in 1 patient.[17] The primary disadvantage of this technic is the need for constant close apposition of the external transmitter and the subcutaneous receiver.

Another way to avoid having the wires from the heart go through the skin is to attach them to a pacemaker buried under the skin. Other workers[18] and we also have built miniature pacemakers containing long-lived batteries for subcutaneous implantation and have demonstrated in dogs the feasibility of this technic. Minor surgery would be necessary to replace

the unit before the batteries fail, at intervals variously estimated at present to be from 1½ to 5 years. In the future even this objection may be overcome by implanting a rechargeable battery and receiver with the pacemaker; at convenient intervals an external radio-frequency transmitter would be used to send a recharging current through the skin. At the present stage of development our rechargeable unit is too large to be buried subcutaneously.

Indications for the Surgical Implantation of Electric Pacemakers

It is to be hoped that the application of an appropriate myocardial electrode together with a subcutaneously implanted pacemaker will eventually provide a technic free of major objections for driving the heart continuously and indefinitely. Until such a technic has been repeatedly demonstrated to be successful and safe for prolonged periods, perhaps a year or more, it should be considered an experimental procedure and reserved for patients in desperate circumstances.

At the present time, therefore, medical measures to prevent recurrent seizures should be given a thorough trial.[19] The sympathomimetic amines (epinephrine, isoproterenol, ephedrine) are most useful when seizures are due to ventricular standstill, since they may arouse, accelerate, and maintain ventricular pacemakers and may also improve atrioventricular conduction. Vagolytic drugs (atropine) should be tried, particularly in patients in whom seizures appear to be related to vagal reflexes. Some recent experiences suggest that corticosteroids[20] or chlorothiazide may also be useful, perhaps through the increased excretion of potassium. There is no satisfactory pharmacologic agent now available for the prevention of Stokes-Adams seizures due to ventricular tachycardia or fibrillation. Drugs that depress ventricular rhythmicity (quinidine, procaine amide, potassium) should not be used; they are contraindicated in patients with complete heart block.

Patients who continue to have frequent seizures despite these measures may be controlled, at least for short periods, with presently available technics of electric stimulation: externally; by an endocardial electrode through a catheter; or by a myocardial electrode placed by percutaneous puncture. For patients who continue to have frequent, severe seizures beyond the limits of these short-term technics, the implantation of a myocardial electrode at thoracotomy may be justified at the present time.

If experiences in these desperate patients are successful, then the indications for this procedure would be broadened. Certainly it would be undertaken in patients who have suffered recent Stokes-Adams attacks despite medical therapy and who could tolerate thoracotomy. Finally, this procedure might at times be indicated to raise the ventricular rate and to improve cardiac function in patients with complete heart block who suffer from limitation of activity and congestive heart failure.

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ARTHUR J. LINENTHAL

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Medicine

I firmly believe that if the whole *materia medica* as now used could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes.—OLIVER WENDELL HOLMES, M.D. From an address to the Massachusetts Medical Society.

Clinical Recognition of Tricuspid Stenosis

By JOSEPH K. PERLOFF, M.D., AND W. PROCTOR HARVEY, M.D.

OPINION differs regarding the accuracy with which a clinical diagnosis of tricuspid stenosis can be made. It has been stated that the recognition of tricuspid stenosis was clinically feasible only in advanced cases,[1] and that the murmurs of tricuspid and mitral stenosis were indistinguishable.[2] Bedside diagnoses were made in 12 of 15 cases in one series,[3] however, and in 11 of 12 cases in another.[4] There is evidence that the incidence of tricuspid stenosis has been underestimated[3-7] suggesting that the lesion, particularly early in its natural history, is still being overlooked. These oversights may contribute to the failure of improvement in some patients after mitral valvulotomy. It must also be noted that in stenosis of the tricuspid valve the transvalvular gradient is commonly small and unless the diagnosis is actively sought for, it can be overlooked during routine venous catheterization. Clinical suspicion of this lesion may thus underlie the success of physiologic studies in establishing the diagnosis and in assessing its severity. It is the purpose of this paper to evaluate the validity of clinical criteria upon which recognition of tricuspid stenosis might be based, emphasizing particularly the physical signs and their mechanisms.

Materials and Methods

Thirteen patients were studied, all personally seen by the authors. Careful attention was directed to the peripheral arterial pulse, to the jugular venous pulse, to palpation of the precordium, and to auscultation of the heart. Five patients were seen at the Georgetown University Hospital, 6 at the Clinic of Surgery of the National Institutes of Health, 1 at the U. S. Naval Hospital, Bethesda, and 1 at Walter Reed Army Hospital. In 12 of the cases the diagnosis of tricuspid stenosis was made clinically either before catheterization or without knowledge of the physiologic data. In the thirteenth case the diagnosis was known beforehand. In one of the earlier patients in this series the diagnosis of tricuspid stenosis was made clinically, was missed at catheterization, but was proved at autopsy.

Aside from routine electrocardiograms, chest x-rays, and fluoroscopy of the heart, venous catheterization was performed in all patients, and left heart catheterization in 9. The diagnoses were further confirmed at surgery in 8 patients, and at autopsy in 2. The physiologic diagnoses of tricuspid stenosis were based principally on the criteria of Killip and Lukas.[8] The most refined technic in our experience consisted of the use of a double-lumen catheter with simultaneous right atrial and right ventricular pressure pulses inscribed from the same base line on a photographic recorder after exercise and during deep respiratory excursions. The transvalvular gradient, exaggerated by exercise, was further magnified during inspiration. It should be emphasized that simple continuous recording of pressure while the catheter was pulled from the right ventricle into the right atrium was a relatively insensitive method and could occasionally miss significant tricuspid stenosis.

In 12 of the 13 patients thoracic wall logarhythmic phonocardiograms were taken with either a 3-channel Cambridge model or a Sanborn Twin-Beam recorder at paper speeds of 50 to 75 mm. per second. In 3 patients intracardiac phonocardiograms were taken with a catheter-tip microphone.* Indirect carotid and jugular venous pressure pulses were taken with a pulse wave amplifier attached to the neck with a suction cup. In 8 patients, simultaneous right atrial and right ventricular pressure pulses were inscribed on a cathode-ray recorder or on a Sanborn Twin-Viso recorder. Simultaneous left atrial and left ventricular pulses were obtained by means of the bronchoscopic technic of left heart catheterization.† Retrograde aortic catheterization for the detection of aortic insufficiency was done in the Clinic of Surgery of the National Heart Institute by the method of Braunwald and Morrow.[9]

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*Manufactured by the American Electronics Company, Philadelphia, Pa.

†The left heart catheterizations were done by Dr. Andrew G. Morrow, Chief, Clinic of Surgery, National Institutes of Health, Bethesda, Md.

Table 1

Clinical Data in Thirteen Cases of Tricuspid Stenosis

Case no.	Sex and current age (yr.)	History of rheumatic fever	Age murmur first noted (yr.)	Age at onset of symptoms (yr.)	Awareness of "A" wave	Effort dyspnea	Syncope	Orthopnea	Nocturnal dyspnea	Acute pulmonary edema	Hemoptysis	Fatigue	Chest pain	Edema, ascites, hepatomegaly, jaundice
1	34 F	Chorea age 12 freq. upper resp. infec.	29	29	—	Mild	—	—	—	—	—	—	Ill-defined	—
2	28 F	Strep. throat and murmur, age 12	12	Asymptomatic	—	—	—	—	—	—	—	—	—	—
3	35 F	Scarlet fever age 10, Subseq. polyarthritis, chorea	Indefinite	10, mild dyspnea	—	Mild to moderate	—	—	—	—	—	+	Innocent mammary-type	—
4	35 F	Age 7, 3 recurrences	20	31	+	Marked	—	+	—	—	+	—	—	Ankle edema, hepatomegaly
5	30 F	Prob. age 13, ARF, age 28	19	24	+	Severe	—	Mild	+	—	—	—	Retrosternal burning	Edema, hepatomegaly
6	27 F	Polyarthritis age 9, chorea age 13	17	"Always" dyspneic	—	Marked	3 Episodes	Mild	—	—	+	+	—	Hepatomegaly, with onset atrial fibr.
7	19 M	—	19	18	+	Mild	—	—	—	—	—	—	Occas. RUQ discomfort on effort	—
8	32 F	Told of rheum. fever age 13	22	13	+	Moderate	—	+	+	—	—	—	—	Ankle edema, mild hepatomegaly
9	23 F	Age 14	16	18	—	Marked	—	+	+	—	+	—	+	Edema, hepatomegaly
10	42 F	Age 7	16	22	+	Moderate	Once	During pregnancy	Twice during pregnancy	—	Freq. bouts during pregnancy	—	—	Mild hepatomegaly
11	29 F	Childhood	Childhood	26	—	Marked	Repeated	+	+	—	—	Since early childhood	—	Edema, ascites, hepatomegaly, pleural effusion
12	28 F	Quest. at age 6, acute arthritis age 22	Not known	26	Questionable before atrial fibr.	Moderate	Dizziness	+	During winter bronchitis	—	Streaked with bronchitis	+	Vague	—
13	32 F	Freq. upper respir. infec., tonsillectomy	"as long as can recall"	29	—	Marked	Effort weakness	+	+	—	—	Easily for past 3 yrs.	—	Edema, ascites, hepatomegaly

Table 2

Case no.	Pure TS	TS with slight TI	TS with moderate TI	PA pressure (mm. Hg)	Rt. atrial pressure (mm. Hg)	Tricuspid gradient (mm. Hg) or orifice size	Pure MS	MS with slight to moderate MI	LA or PCVP (mm. Hg)
1	+			16/6 (12)*	A 13-16 V 3-5	4-5	—	—	Post exercise PCVP 0
2	+			20/10 (13)	A 14-17 V 7-9	3-4	—	—	Post exercise PCVP 0
3	+			20/6 (11)	A 11 V 3-4	5-6	—	—	LA (6
4		+		50/25 (33)	A 10-12 V 3-4	5	+		LA (2)
5		+		100/50 (67)	A 30-35 V 20-25	Fingertip	+		PCVP (20)
6			+	39/19 (25)	A 10 V 7	2 cm.^{2}	+		
7	+			25/10 (15)	A 18-20 V 5-7	3-4	+		LA (20)
8	+			32/10 (17)	A 10-12 V 3-4	Surgery, fingertip	+		A 25 V 12
9			+	85/40 (55)	A 16-20 V 14-19	5		Moderate	A 35 V 40
10	+			42/23 (27)	A 11 V 4	5	+		LA (21)
11	+			66/32 (44)	Atrial fib. V 15-19	.53 cm.^{2}		Slight	LA (30)
12		+		24/10 (18)	A 11-13 V 6	4-5		Slight	A 12 V 10 (8)
13	+			67/41 (50)	Atrial fib. (9)	5 Autopsy, orifice 1½ fingers	+		PCVP (22)

*Figures in parentheses represent the mean value.

Abbreviations: TS, tricuspid stenosis; TI, tricuspid insufficiency; PA, pulmonary artery; MS, mitral stenosis; MI, mitral insufficiency; LA, left atrial; PCVP, pulmonary capillary venous pressure; AS, aortic stenosis; AI, aortic insufficiency. A = "a" wave; V = "v" wave.

Results

Age and Sex

There were 12 women and 1 man, ranging in ages from 19 to 42 years, with a mean age of 30 years.

History

There was a convincing history of antecedent rheumatic fever in 9 cases, a suggestive history in 3 cases (1 had chorea alone), and no historical evidence of rheumatic fever in 1 other case. One patient was completely asymptomatic, 5 patients were slightly to moderately symptomatic, 5 were markedly symptomatic, and 2 were incapacitated. The classic picture of tricuspid stenosis in the disabled, fibrillating patient with hepatomegaly, jaundice, edema, and ascites, was present in only 2 instances. The distribution and frequency of specific cardiovascular symptoms are seen in table 1.

Associated Valve Lesions

Coexisting mitral valve disease was present in all except 1 case, and the aortic valve was involved in all except 2. The tricuspid valve was purely stenotic in approximately half the cases (table 2). In 1 case studied clinically, physiologically, and at autopsy, it appeared that the presence of pulmonary hypertension

Physiologic Data in Thirteen Cases of Tricuspid Stenosis

Mitral gradient (mm. Hg) or orifice size	TS>MS	Pure AS	Pure AI	AS and AI	Aortic gradient (mm. Hg) or orifice size	Cardiac Index (L./Min./M.² BSA)
	+		Moderate			Rest 1.7 Exercise 1.6
	+		Mild			Rest 2.5 Exercise 5.0
	+		Moderate			Rest 2.0 Exercise 2.6
15				AS, trivial AI	70	Invalid
Surgery, less than fingertip				AS, trivial AI		Invalid
0.9 cm.²				Significant AI	45	Rest 1.7 Exercise 1.7
6		Moderate			40	Rest 2.5
Surgery, less than fingertip			Moderate			Rest 1.9
18						Rest 1.6
14		Slight				Rest 2.0
1 cm.²	+	Severe		AS, trivial AI	0.3 cm.²	Rest 1.5 Exercise 2.0
10						Invalid
Autopsy, orifice fingertip				AS, trivial AI	Autopsy, orifice less than fingertip	Rest 1.66

had caused an anatomically stenotic tricuspid valve to become insufficient as well. This patient had the highest pulmonary arterial pressure in the series (100/50, mean 67). In a second case, considered to have mild, pure tricuspid stenosis, the valve became insufficient after the onset of rapid, atrial fibrillation and right ventricular failure, an observation similar to the experience of others.[10] In 4 cases, the tricuspid stenosis was estimated to be of greater hemodynamic severity than the mitral stenosis, an incidence approximating that of Gibson and Wood.[3] One of these patients had a calculated tricuspid orifice smaller than the calculated mitral orifice with surgical confirmation of these impressions. The other 3 patients (all of whom demonstrated mild to moderate aortic insufficiency) had normal postexercise mean left atrial pressures. One had no detectable transvalvular mitral gradient and no fluoroscopic evidence of left atrial enlargement. No patient in this series had isolated tricuspid stenosis. Only 5 instances of this occurrence were found in the literature.[3-5, 11, 12]

Jugular Venous and Right Atrial Pressure Pulses

The jugular venous pulse was analyzed at the bedside according to the following method,

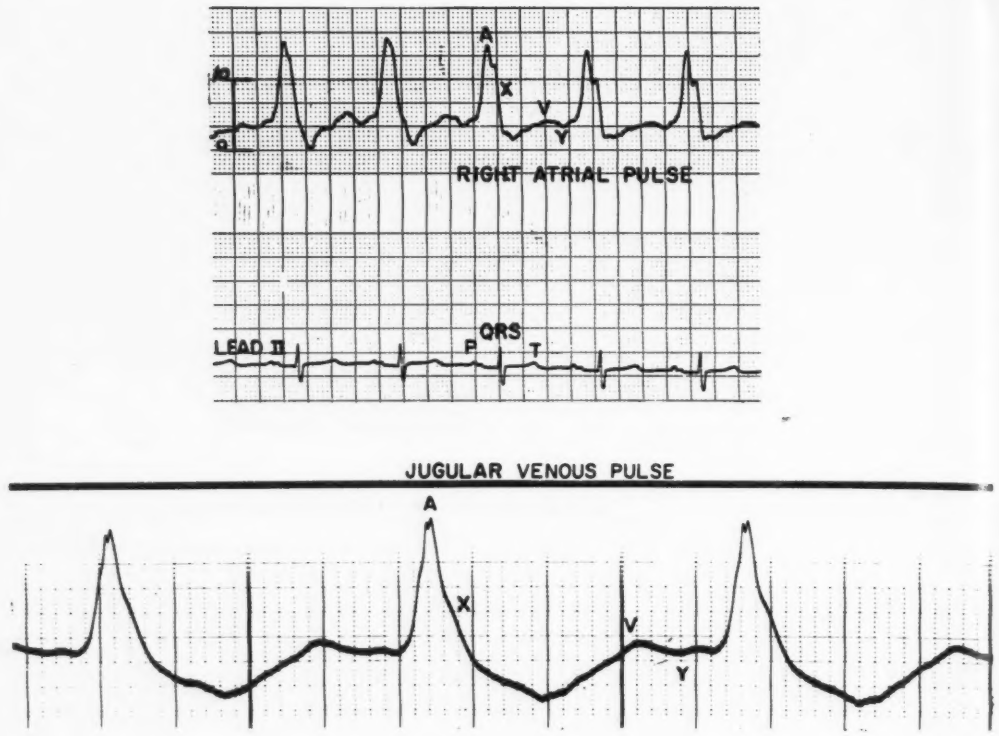

Figure 1A

A woman, age 34, with tricuspid and mitral stenosis. The right atrial and jugular venous pulses are similar in contour and illustrate the large "A" wave, small "V" wave, and gentle "Y" descent.

without which correlation with the right atrial pulse was occasionally poor.[13, 14] The internal jugular vein was observed with the upper half of the patient's body elevated to the point that allowed the vein to empty and fill with the greatest amplitude (average 25° to 35° from horizontal). The contralateral carotid artery was gently palpated for timing purposes. The patient's head was rotated slightly toward the side of observation in order to relieve tension of the sternocleidomastoid on the underlying internal jugular vein. Of the 11 patients with sinus rhythm the "A" waves were giant in 5, marked in 6, and modest in none (table 2 and fig. 1*A*). These represented right atrial "A" waves of 14 to 20 mm. Hg in 4 of the patients with giant "A" waves, 30 to 35 mm. Hg in the fifth patient, and 10 to 13 mm. Hg in the 6 patients classified as marked. The V waves were inconspicuous, and the Y descents imperceptible except in 2 cases with pulmonary hypertension and right ventricular failure. Each of the 12 patients with established atrial fibrillation had an elevated V wave with a gentle Y descent, and the patient who began to fibrillate several weeks after catheterization had a similar jugular venous pulse (fig. 1*B*).

Pulmonary Arterial Pressure

In 6 patients the mean pulmonary arterial pressure was between 10 and 20 mm. Hg, in 3 between 20 and 35 mm. Hg, and in the remaining 4 it was 44, 50, 55, and 67 mm. Hg (table 2). In the latter 4 patients the mean left atrial pressures were 30, 22, 32, and 20 mm. Hg, respectively.

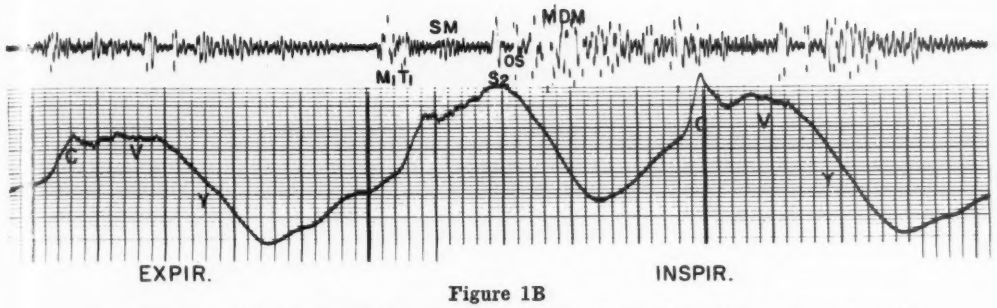

Figure 1B

A woman, age 28, with trivalvular stenosis and atrial fibrillation. Jugular venous pulse illustrates gentle "Y" descent. Synchronous phonocardiogram at lower left sternal edge.

Palpation of the Precordium[15, 16]

A right ventricular lift was conspicuous in 3 patients, and moderate in a fourth, who developed increasing congestive heart failure after the onset of atrial fibrillation. The sound of pulmonary valve closure was palpable in only 2 instances. A lower left sternal edge diastolic thrill, which either appeared or increased with inspiration, was present in 4 cases. Palpation of the left ventricle and of mitral and aortic thrills varied with the coexisting valvular diseases.

Auscultatory and Phonocardiographic Findings

The first heart sound was obviously accentuated in 7 cases, moderately accentuated in 3, and within normal limits in 3. In the case with no evident mitral valve disease, mitral valve closure was of normal intensity and tricuspid closure was moderately increased. The first sound was single in 6 instances and was split into mitral and tricuspid valve components[17] in 7 instances. The second heart sound was single in 10 instances, and split into pulmonic and aortic components in 3 instances. One of these latter cases had aortic stenosis and the second sound was paradoxically split.[18] In 3 instances, the single second sound in the second left interspace was sufficiently loud to suggest pulmonary hypertension. An additional sound consistent with the opening snap of the tricuspid valve was recorded in 2 patients (fig. 2) but was not appreciated by auscultation. Identification of this sound was based on the following criteria: (1) its occurrence 0.06 to 0.07 second after pulmonary valve closure, an interval corresponding to the estimated duration of right ventricular isometric diastole, (2) the failure of the interval between the single second sound and the additional sound to increase with inspiration as it might if these events were aortic and pulmonic valve closures, (3) the identification of normal inspiratory splitting and expiratory synchrony of the second sound in 1 of the 2 patients, and (4) the identification in both patients of a separate later sound with the timing of a mitral opening snap. The precedence in the cardiac cycle of tricuspid over mitral opening snap (first and fourth criteria) is at variance with statements of others[10] and is based on the following observations. In the dog, isometric right ventricular diastole (the interval between closure of the pulmonary valve and opening of the tricuspid) is significantly shorter than isometric left ventricular diastole (the interval between closure of the aortic valve and opening of the mitral).[19] The sequence of events of the cardiac cycle in the dog and in man is generally similar.[20] Finally, the opening sound of the tricuspid valve that is believed to occur occasionally in atrial septal defect [21, 22] has an early timing consistent with the foregoing contentions.

In all patients the diastolic murmur of tricuspid stenosis was appreciated. This murmur was presystolic, with absent or trivial mid-diastolic components in the patients with sinus rhythm (fig. 3) and was mid-diastolic (rapid flow phase) in the 3 patients with

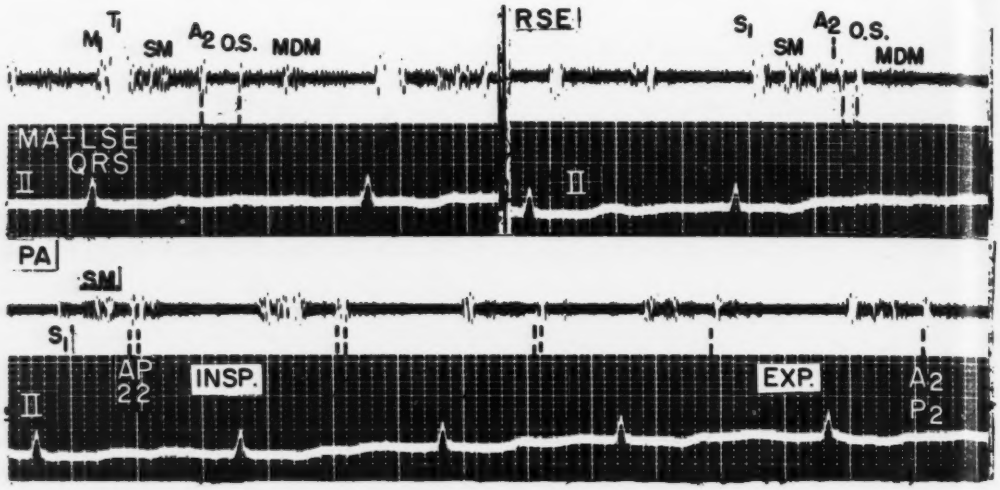

Figure 2

A woman, age 29, with atrial fibrillation, trivalvular stenosis, and slight aortic insufficiency. Upper left tracing recorded between apex and lower left sternal edge: opening snap (OS) considered to be mitral. Upper right tracing recorded at lower right sternal edge: opening snap (OS) considered to be tricuspid. Lower tracing recorded at pulmonic area (PA) to illustrate inspiratory splitting of aortic (A_2) and pulmonic (P_2) components of the second heart sound.

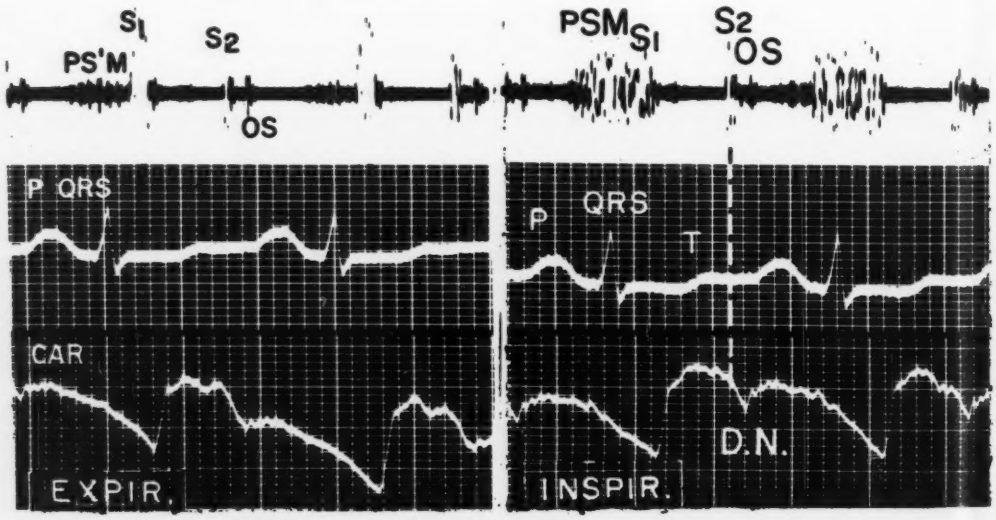

Figure 3

A woman, age 32, with tricuspid stenosis, mitral stenosis, and pure aortic insufficiency. Note inspiratory augmentation of the presystolic murmur. Phonocardiogram recorded at the lower left sternal edge. PSM, presystolic murmur; S_1, first heart sound; S_2, second heart sound; OS, opening snap (here thought to be mitral); CAR, carotid pulse; DN, dicrotic notch.

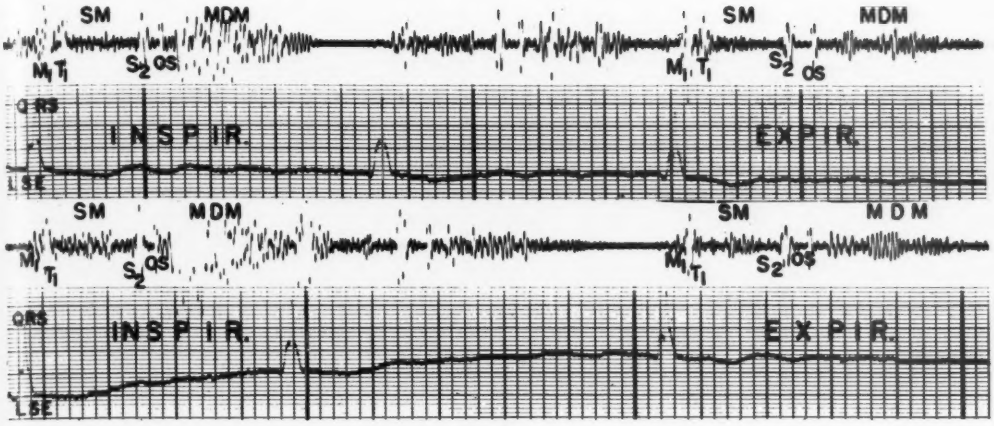

Figure 4

A woman, age 28, with atrial fibrillation, trivalvular stenosis, and trivial aortic insufficiency. Note inspiratory augmentation of the mid-diastolic murmur. Phonocardiogram recorded at the lower left sternal edge. M_1, mitral component of the first heart sound; T_1, tricuspid component of the first heart sound; S_2, second heart sound; OS, opening snap; SM, systolic murmur; MDM, mid-diastolic murmur.

atrial fibrillation (fig. 4). It was best heard at the lower left sternal edge, especially the fourth intercostal space, but occasionally in the third or fifth intercostal spaces. It characteristically increased during inspiration and decreased during expiration. The increment of change was often 2 to 3 grades. In several instances the murmur was virtually inaudible during expiration, but was grade III during inspiration. The mitral stenotic murmur was heard best at the cardiac apex. When the stethoscope was "inched" from this area to the left sternal edge, there was often an auscultatory hiatus in which the murmur of mitral stenosis became faint or absent, followed by the appearance of the murmur of tricuspid stenosis as the left sternal border was reached.

Intracardiac phonocardiograms (fig. 5) done on 3 patients revealed that the murmur was absent when the microphone was located on the atrial side of the tricuspid valve, but was grossly apparent when the catheter tip was advanced to the right ventricular side of the valve, where it occupied a position in the direction of turbulent flow. The murmurs recorded in the right ventricular cavity distal to the tricuspid valve increased with inspiration and decreased with expiration. They differed from the thoracic wall phonocardiograms in 2 respects: (1) the increased intensity of the presystolic component, and (2) the appearance of a mid-diastolic component.

Hemodynamic Observations

Simultaneous right atrial and right ventricular pressure pulses were recorded in 8 patients in this series, 6 with sinus rhythm (fig. 6), and 2 with atrial fibrillation (fig. 7). Simultaneous left atrial and left ventricular pressure pulses were recorded* in 5 additional patients with mitral stenosis, (3 with sinus rhythm, and 2 with atrial fibrillation) 1 of which was in this series. The tricuspid transvalvular gradient increased with inspiration and decreased with expiration. In 5 cases this was due both to a fall in right ventricular diastolic pressure and to a concomitant rise in right atrial pressure. In 2 cases it was due principally to a fall in right ventricular diastolic pressure, the right atrial pressure remaining unchanged or falling only slightly. In 1 case the gradient increased due to a rise

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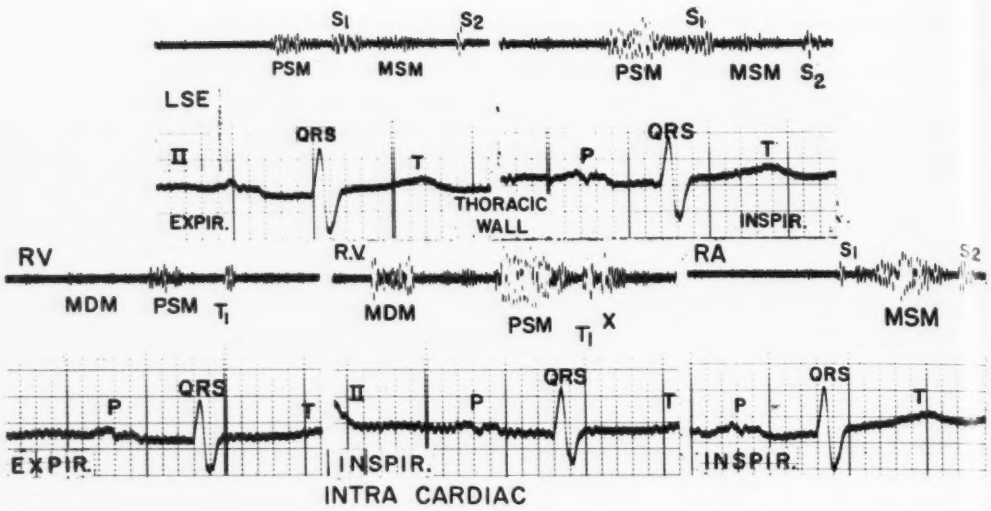

Figure 5

A woman, age 34, with tricuspid and mitral stenosis. Upper tracings are thoracic wall phonocardiograms recorded at the lower left sternal edge (LSE) to illustrate inspiratory increase of the presystolic murmur (PSM). Lower series are intracardiac phonocardiograms. With the microphone in right ventricle (RV) the mid-diastolic and presystolic murmurs increase with inspiration. In the right atrium (RA) no diastolic murmur is recorded even during inspiration. The MSM is a midsystolic murmur across a stenotic aortic valve, well recorded in RA because of its anatomic proximity to the aorta. "X" is an artifact.

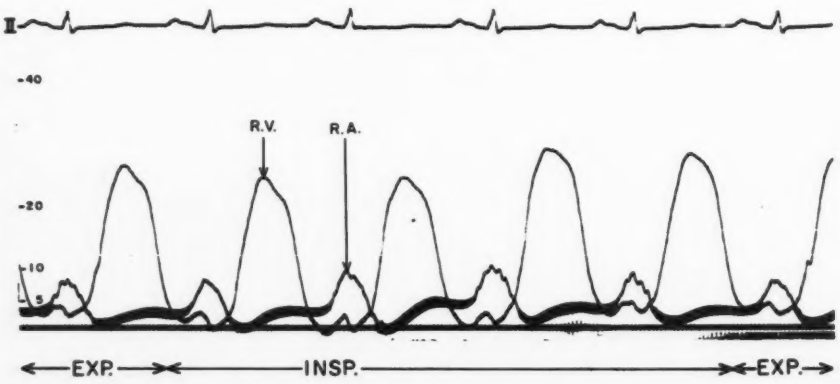

Figure 6

A woman, age 32, with tricuspid and mitral stenosis, and pure aortic insufficiency. Note selective inspiratory increase in tricuspid transvalvular gradient due to concomitant rise in right atrial (RA) pressure and fall in right ventricular (RV) pressure. RA and RV pressure pulses recorded simultaneously through a double-lumen catheter. (Courtesy, Dr. Andrew G. Morrow.)

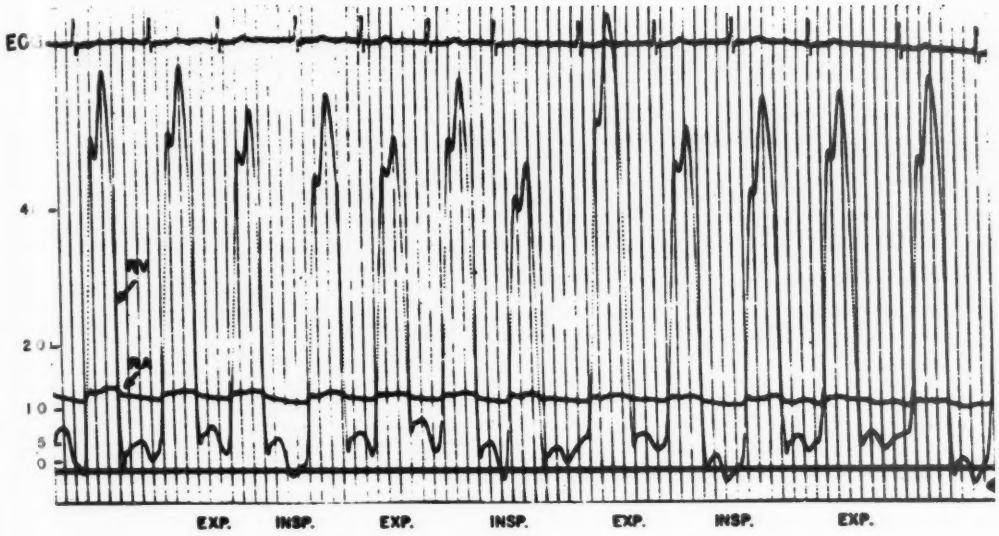

Figure 7

A woman, age 29, with atrial fibrillation, trivalvular stenosis, and slight aortic insufficiency. The inspiratory fall and expiratory rise in right ventricular (RV) diastolic pressures are not paralleled by pressure changes of equal magnitude in the right atrium (RA), resulting in an inspiratory increase and expiratory decrease in tricuspid transvalvular gradient. The RA and RV pulses were recorded simultaneously through a double-lumen catheter. (Courtesy, Dr. Andrew G. Morrow.)

in right atrial pressure without change in right ventricular diastolic pressure. When similar pulses were recorded in 3 cases with the chest opened during surgery, these respiratory variations in transvalvular gradient failed to occur. The diastolic gradient across the *mitral* valve remained *unchanged* during the respiratory cycle, since the inspiratory and expiratory changes in the left atrial and left ventricular diastolic pressures were of equal magnitude (fig. 8).

The Electrocardiogram (fig. 9)

Eleven cases had sinus rhythm (1 patient began to fibrillate under observation) and 2 had established atrial fibrillation. Electrocardiographic evidence of right ventricular hypertrophy was unequivocably evident in none of the patients, although 4 had vertical electrical axes. Left ventricular hypertrophy occurred in 4 instances, and an additional patient had left axis deviation. When atrial enlargement was diagnosed according to the criteria of P-wave amplitude,[23] P-wave configuration,[24] or P/P-R ratio,[25] isolated right atrial enlargement was present in 3 of the cases, and biatrial enlargement was present in 7 cases. One patient had a QR pattern in V_1, suggesting right atrial enlargement based on the observations of Sodi-Pallares.[26]

X-rays (fig. 10)

The posteroanterior projection was found to be the most rewarding.[3] In this view the portion of the right cardiac contour occupied by the right atrium was moderately to markedly enlarged, and the portion of the left cardiac contour occupied by the pulmonary artery segment was only slightly to modestly enlarged. Calcification of the tricuspid valve was not identified in any case.

Discussion

Although the reported incidence of tricuspid stenosis[3, 7] does not necessarily reflect the frequency with which this lesion is of hemo-

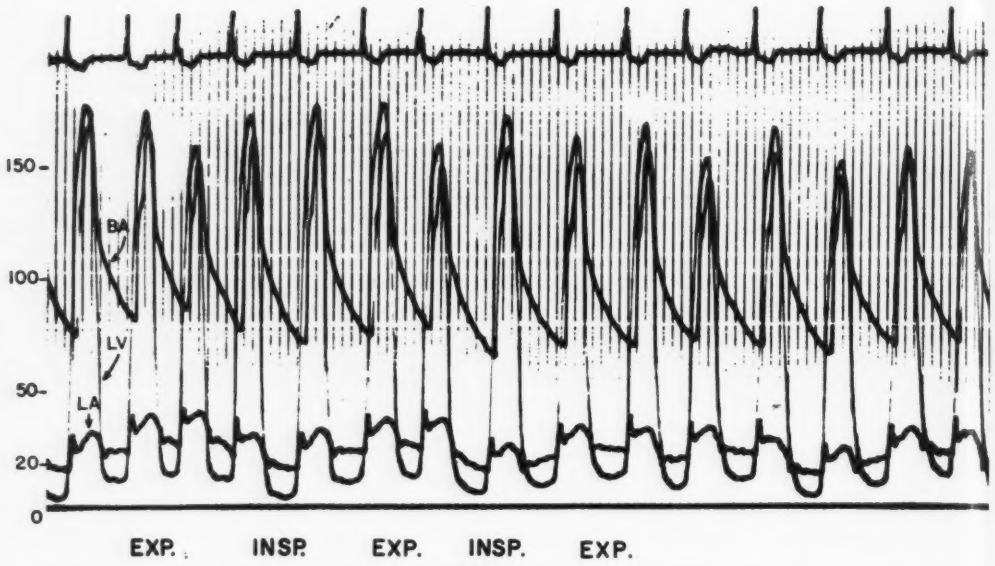

Figure 8

A woman, age 28, with mitral stenosis and mild aortic stenosis. The inspiratory fall and expiratory rise in diastolic pressure in the left ventricle (LV) is paralleled by pressure changes of equal magnitude in the left atrium (LA) leaving the mitral transvalvular gradient unchanged during respiration. BA, brachial artery. (Courtesy, Dr. Andrew G. Morrow.)

dynamic significance, our data do suggest that proper assessment of physiologic severity often depends upon the initial clinical index of suspicion. Careful attention to the history, to the entire spectrum of physical signs, to the electrocardiogram, and to the x-ray, should allow a confident diagnosis in a substantial majority of cases.

The first feature that might arouse suspicion is the history in a patient with mitral stenosis, who, although perhaps dyspneic and orthopneic, displays a relative paucity of acute paroxysmal symptoms such as pulmonary edema, paroxysmal nocturnal dyspnea, and the pulmonary apoplexy type of hemoptysis.[14] This could result from an attentuating effect of the tricuspid obstruction on *abrupt* increases in blood flow into the lesser circulation. This assumption might also underlie previous observations that in more advanced cases of tricuspid stenosis incapacity may not be so pronounced as one would expect from the recurrent hepatomegaly, ascites, and edema.[27] Although the suggestion of the "protective" role of the stenotic tricuspid valve has been commented upon,[2, 7] it appears that from the symptomatic point of view it may be the *paroxysmal* features of pulmonary symptomatology that are most frequently attenuated.

It is in the physical signs, however, that the highest index of suspicion is aroused. The peripheral arterial pulse (brachial and carotids were routinely palpated) was of interest in two respects. First, to emphasize that the prominent pulsation seen in the neck was venous and not arterial, and second, to detect evidence of aortic insufficiency (especially the pulsus bisferiens[28]) as an aid in distinguishing a left parasternal early diastolic murmur from a Graham-Steell. The pulse most rewarding to analyze was that seen in the *internal* jugular vein. The typical tricuspid stenotic jugular venous pulse with sinus rhythm (fig. 1*A*) consisted of an "A" wave of unusual magnitude, occasionally reaching

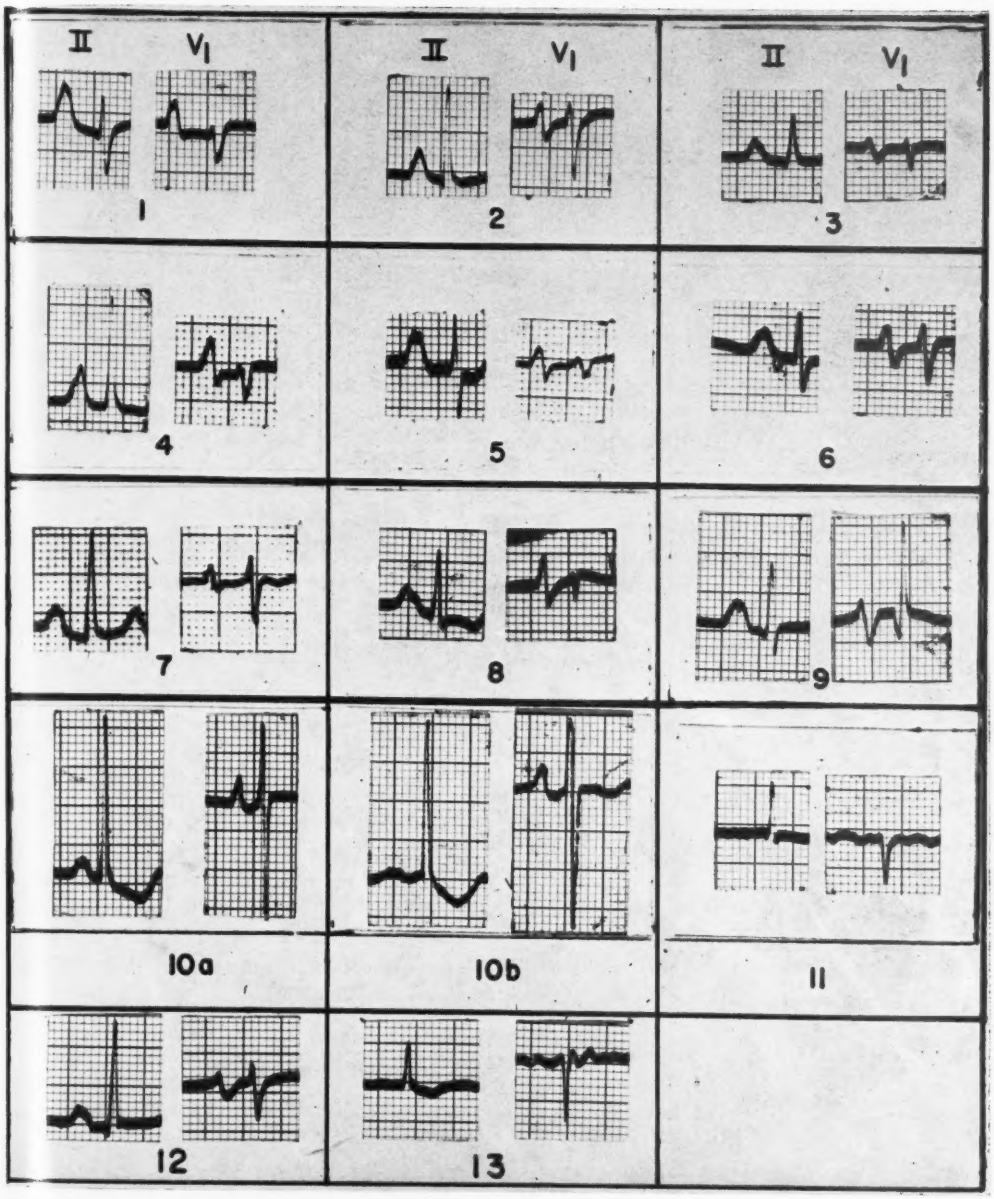

Figure 9

Note evidence of right atrial enlargement in lead II and negative evidence of right ventricular hypertrophy in lead V_1. In no. 9 the QR in V_1 suggests right atrial enlargement according to criteria of Sodi-Pallares. In 10a and 10b (from the same patient) right atrial enlargement was difficult to assess because of changing P-wave configuration and P-R relationship.

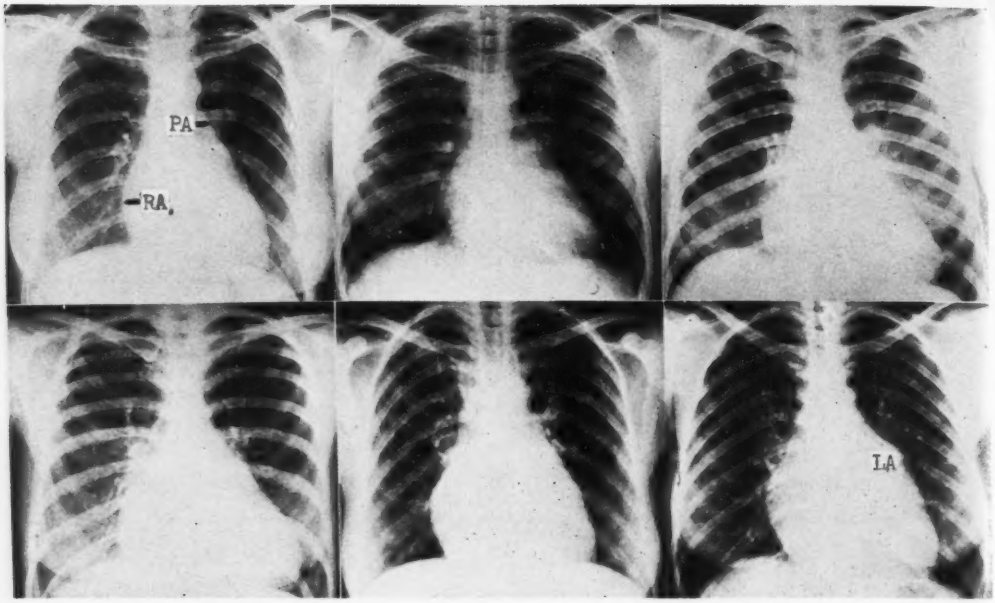

Figure 10

Six representative x-rays (cases 2, 7, and 5 (upper); *cases 4, 10, and 8* (lower)*) illustrating mild to marked enlargement of the right atrial contour (RA) associated with only modest enlargement of the pulmonary artery segment (PA). Left atrial appendage (LA).*

the angle of the jaw, a small "V" wave, and a gentle, usually imperceptible "Y" descent.[3] The patient may report awareness of this large venous pulse, which may become still more conspicuous during effort or excitement. Although it has been said that a giant "A" wave is of limited value in the diagnosis of tricuspid stenosis because of its occurrence in other conditions,[4] we think that analysis of this pulse configuration in proper context can alone be virtually diagnostic of tricuspid valvular obstruction.[3, 29] In an acyanotic patient isolated "A" waves of giant proportion unassociated with "V"-wave elevation or increased rate of fall of the "Y" descent are seen only if the right atrium contracts against a resistance at the tricuspid orifice, or if it contracts against the resistance offered by a severely hypertensive but nonfailing right ventricle. If this pulse contour is observed, therefore, the diagnosis of tricuspid stenosis, pulmonary stenosis, or pulmonary hypertension can immediately be suspected. Pulmonic stenosis should cause no confusion in the cases under consideration. In the presence of pulmonary hypertension of sufficient severity to generate the giant "A" wave, one almost invariably can feel a heaving lift of the right ventricle in the third and fourth intercostal spaces along the left sternal edge, and a palpable shock of accentuated pulmonary valve closure.[30] The finding of an isolated, dominant giant "A" wave in the jugular venous pulse unassociated with either a palpable right ventricle, a palpable pulmonary second sound, or a thrill of pulmonic stenosis, is in itself strong presumptive evidence that the resistance generating the "A" wave is at the level of the tricuspid valve. The availability of this sign is emphasized by the frequency with which sinus rhythm occurred when the diagnosis of tricuspid stenosis was made relatively early in the course of the disease. With atrial fibrillation analysis of the jugular ve-

nous pulse is still valuable but more difficult to assess. The stenotic tricuspid valve elevates the right atrial pressure and impedes its rate of fall in a manner analogous to the effect of mitral stenosis on the left atrial pressure pulse.[31] Hence, an elevated "V" wave and a gentle "Y" descent in the jugular venous pulse are the only clues of tricuspid stenosis in the presence of atrial fibrillation (fig. 1*B*).

At this point in the physical examination one should carry palpation of the precordium to the lower left sternal edge to seek the tricuspid stenotic thrill. The fingertips should explore the area carefully being aware that the thrill not only may be exceedingly limited in location, but typically will increase with inspiration and decrease with expiration.

Auscultation is the most important phase of the examination and is even more rewarding when applied with the heightened index of suspicion allowed by the foregoing physical signs. Evidence of dominant mitral stenosis is almost always present. It appears that tricuspid stenosis occurs so uncommonly with dominant mitral insufficiency that the diagnosis of this combination should be considered with caution.[3] The first heart sound at the cardiac apex and lower left sternal edge was either moderately accentuated or normal in 6 of the 13 cases. Absence of consistent, obvious accentuation may be related to the relatively frequent prolongation of P-R interval (fig. 9) associated with the right atrial enlargement[25] of tricuspid stenosis. The first heart sound was often split (7 instances) probably due to concomitant delay in *both* mitral *and* tricuspid components (figs. 2 and 4). It is important to distinguish the tricuspid component of the first heart sound from a pulmonic ejection sound,[32] which might occur with pulmonary hypertension. The ejection sound is high-pitched, clicking, best heard in the pulmonary area or subjacent intercostal space, and often decreases with inspiration and increases with expiration.

The second heart sound in tricuspid stenosis is important in two respects. Firstly, the intensity of the pulmonic component or the cumulative intensities of synchronous aortic and pulmonic components heard in the second left intercostal space should be used as evidence for or against pulmonary hypertension. Since aortic insufficiency is not uncommonly associated with tricuspid stenosis, the differentiation of the murmurs of aortic and pulmonic insufficiency should be re-emphasized. Secondly, in this series of cases respiratory splitting of the second heart sound occurred in only 3 instances. This suggests that in the presence of tricuspid valve obstruction the inspiratory augmentation of right ventricular filling may be impeded, and hence the inspiratory increase in right ventricular stroke volume and the inspiratory delay in pulmonary valve closure may not readily occur.[33]

Following the second heart sound the tricuspid opening snap[34] may be generated (fig. 2). Because the value of this sign has been emphasized,[35] it was repeatedly sought for, but not convincingly appreciated by auscultation in any of our cases. It was, however, considered to have been recorded in two instances. Although the opening snap of the tricuspid valve can thus occasionally be recorded, its value in the clinical diagnosis of tricuspid stenosis is likely to be limited.

The most important auscultatory sign is the tricuspid stenotic murmur itself. Our studies suggest that in the majority of cases this murmur can be clearly distinguished from the accompanying murmur of mitral stenosis. Auscultation should begin at the cardiac apex, where the murmur of mitral stenosis is most evident, and proceed in small increments toward the lower left sternal edge. The mitral murmur will often fade between the apex and left sternal edge before the tricuspid murmur becomes evident. The area where the murmur of tricuspid stenosis should be sought is, then, along the *lower left sternal edge,* usually localized to the fourth or fifth intercostal spaces, but occasionally heard in the third interspace. It is imperative to emphasize this point, since it is still generally stated[36] that the tricuspid area is along the right sternal edge or over the xiphoid. The anatomic position of the tricuspid valve, especially in the presence of right

atrial enlargement, together with the right-to-left direction of the jet across this stenotic valve, make the lower left sternal edge the appropriate area for auscultation of the murmur of tricuspid stenosis.[4] Since the area in which the murmur is appreciated might be exceedingly limited, a careful geographic search of the region must be made.

In those cases of sinus rhythm the murmur was predominantly, if not exclusively, presystolic (fig. 3). A mid-diastolic component was either trivial or absent, although recordable with an intracardiac microphone in the right ventricle (fig. 5). Since the P-R interval is commonly prolonged in tricuspid stenosis, probably reflecting right atrial enlargement,[25] the presystolic murmur is often remarkably discrete. The patient in this series in whom the auscultatory diagnosis of tricuspid stenosis was most difficult was the only one with a short P-R interval resulting in a very brief period between onset of presystolic murmur and first heart sound (fig. 9, parts 10a and 10b). In atrial fibrillation the tricuspid stenotic murmur begins earlier in diastole during the rapid flow phase (fig. 4). It may then continue with decreasing intensity up to the subsequent first heart sound.

The quality of the murmur of tricuspid stenosis was not uncommonly indistinguishable from that of the mitral stenotic murmur, but one occasionally got the impression that the tricuspid murmur was more superficial and higher pitched than the murmur of mitral stenosis.[4, 10] However, the only consistently reproducible way to distinguish these two stenotic murmurs was to analyze their respective variations in intensity during inspiration and expiration (figs. 3 and 4). Carvallo, in 1950,[34] applied his observations on tricuspid insufficiency to the murmur of tricuspid stenosis, stating "the maneuver consists of making the patient inspire deeply and then hold the breath in post inspiratory apnea. This produces an increase in the intensity of the diastolic murmur." It is this inspiratory augmentation of intensity that is the most valuable auscultatory sign in the diagnosis of tricuspid stenosis.[3, 4] It should be pointed out, however, that the most productive method of eliciting this sign is by listening while the patient is instructed to undertake moderately deep, slow, but *continuous* respiratory excursions. If the breath is held for any length of time in either inspiration, expiration, or in the respiratory mid-position, the sign may be lost. Although Carvallo's basic observation is abundantly valid, it is during the active inspiratory effort that the murmur increases in intensity, and if the breath is held in inspiratory apnea the intensity may fade. The inspiratory augmentation may be of the magnitude of two or three grades, and not uncommonly may be grade III on inspiration but virtually inaudible on expiration. The intensity increase may be present for a series of cycles, or it may occur for only one or two beats at the very onset of inspiration. Since occasionally all auscultatory events increase with inspiration, it must be emphasized that it is the *selective* inspiratory augmentation of the murmur that is peculiar to tricuspid stenosis. This must occur *without* an increase in other acoustic events unless there is coexisting tricuspid insufficiency, in which case *both* tricuspid murmurs will wax and wane with respiration.

It has been stated[10] that with the severest degree of tricuspid stenosis systemic venous pressure may already be so excessive that the inspiratory increase might be inconsequential, thus leaving the murmur uninfluenced by respiration. That this need not necessarily be a consequence of severity is suggested by observations in this and in other studies,[4] indicating that the inspiratory increase in tricuspid gradient can be due solely to a fall in right ventricular diastolic pressure, the right atrial pressure remaining unaltered. The murmur of mitral stenosis either remains unchanged or gets fainter during inspiration. An exception to this might be the patient with mitral stenosis and marked sinus arrhythmia. With shortening of the diastolic filling period during the inspiratory increase in cardiac rate the mitral stenotic murmur might increase just as it increases when the rate is accelerated by other maneuvers.[37] Oc-

casional instances have been reported in which the mitral stenotic murmur has increased with inspiration.[10, 38] If it is assumed that tricuspid stenosis had not been overlooked in these cases and that this inspiratory augmentation was not associated with a sinus arrhythmia or accompanied by increased intensity of other auscultatory events, an explanation is not readily forthcoming. This discrepancy is, however, likely to be an uncommon occurrence.

The mechanism underlying the inspiratory increase in the murmur of tricuspid stenosis as opposed to the murmur of mitral stenosis was considered in the following fashion. All structures in the thorax should share equally the respiratory variations in *intrathoracic* pressure.[39] Therefore, during inspiration as the pressure in the cardiac chambers decreases, the pressure in the right side of the heart falls below that in the *extrathoracic* systemic veins, but the pressure in the left side of the heart falls equally with that in the *intrathoracic pulmonary* veins. Hence, there is a selective inspiratory increase in *systemic* venous filling pressure and a selective inspiratory increase in *right* heart filling. This is thought to be the major cause of the increase in the right ventricular stroke volume that gives rise to the delay in pulmonary valve closure, resulting in normal inspiratory splitting of the second heart sound.[40]

In tricuspid stenosis the inspiratory increase in right ventricular filling is altered by the valvular obstruction. When simultaneous right atrial and right ventricular pressure pulses are recorded through a double-lumen catheter, the transvalvular gradient is seen to increase during inspiration and to decrease during expiration (figs. 6 and 7). Since the inspiratory increase in gradient occurs in the presence of a constant orifice size, there must be an inspiratory increase in transvalvular flow, which is reflected in the inspiratory increase in tricuspid stenotic murmur.[8, 41] As an augmented volume of blood enters the right atrium during inspiration, the stenotic lesion impedes its free entry into the right ventricle. Therefore, the pressure in the right atrium instead of falling in parallel with the diastolic pressure in the right ventricle, either falls only slightly, remains unchanged, or increases. These alterations were observed with either sinus rhythm or atrial fibrillation. When the respiratory fluctuations of intrathoracic pressure were abolished by opening the chest at operation, the respiratory effect on the tricuspid transvalvular gradient was abolished.

Further to establish that the diastolic stenotic murmur which possesses the property of selective inspiratory augmentation was located at the tricuspid orifice, 3 patients were studied by intracardiac phonocardiography (fig. 5). With the microphone lying in the right atrium no murmur was recorded, but when the microphone was advanced to a point just distal to the tricuspid valve, the stenotic murmur was grossly apparent, identifying it as tricuspid in origin. Respiratory tracings revealed that this murmur increased with inspiration and decreased with expiration in a fashion similar to what was considered to be the tricuspid stenotic murmur recorded by the thoracic wall microphone. In an application of the foregoing reasoning to the mitral valve, simultaneous left atrial and left ventricular pressures were recorded in the closed chest in 5 patients with mitral stenosis, 3 with sinus rhythm, and 2 with atrial fibrillation. The inspiratory fall and expiratory rise in intrathoracic pressure were reflected in these pulses with equal magnitude (fig. 8). Even though there were considerable respiratory changes in left ventricular diastolic and left atrial pressures, there was no change in transvalvular gradient. This is in accord with the observation that the mitral stenotic murmur does not selectively increase with inspiration.

Although the commonest cause of tricuspid stenosis is rheumatic fever (table 1), the lesion has been reported as a consequence of carcinoid,[42] endocardial fibroelastosis,[43] endomyocardial fibrosis,[44] and systemic lupus erythematosus.[3] In the presence of a normal valve the orifice may be obstructed by such a lesion as myxoma of the right atrium, which has

been reported to produce a murmur apparently identical in its respiratory variations with the murmur of organic tricuspid stenosis.[45]

Not all tricuspid diastolic murmurs are caused by valvular obstruction. Flow murmurs across the tricuspid orifice may occur in atrial septal defect,[21] but do not wax and wane with respiration. Occasionally rapid atrioventricular flow in the presence of tricuspid incompetence may generate a tricuspid diastolic murmur,[46] a situation analogous to the short mitral diastolic murmur in some cases of pure mitral incompetence.[47, 48] Fascinating in concept is what has been called the "right-sided Austin Flint" murmur in cases of pulmonary insufficiency.[49] Finally, in some cases of right ventricular hypertrophy *without* tricuspid incompetence a diastolic rumble has been described for reasons yet poorly defined.[50]

The clinical diagnosis of tricuspid stenosis rests most securely on the physical signs. The electrocardiogram and x-ray were important, however, from confirmatory points of view. In evaluation of the large "A" wave in the jugular venous pulse it is necessary to exclude significant right ventricular hypertension. Absence of electrocardiographic evidence of right ventricular hypertrophy assists in this exclusion. The most consistent electrocardiographic pattern was the combination of negative evidence of right ventricular hypertrophy in lead V_1, and positive evidence of right atrial enlargement in lead II (fig. 9). The most rewarding x-ray was the simple posteroanterior view (fig. 10). The combination of only slight to modest enlargement of the pulmonary artery segment associated with the contour of an enlarged right atrium along the lower cardiac silhouette was of value in suggesting that the right atrial enlargement was not due to significant pulmonary hypertension, and hence was of further help in assessing the large "A" waves.

In consolidation of the features in the foregoing discussion attention should be directed to the following points in the clinical recognition of tricuspid stenosis: (1) the patient is usually female, commonly considered to have rheumatic mitral stenosis; (2) there is a relative paucity of paroxysmal pulmonary symptoms, and occasionally the patient may be aware of the pulsating "A" wave in the neck; (3) examination of the jugular venous pulse in sinus rhythm reveals an abnormally large, often giant, "A" wave, a shallow "V" wave and gentle "Y" descent, or in atrial fibrillation reveals an elevated "V" wave with a gentle "Y" descent, these occurring in the absence of the physical, electrocardiographic, or radiologic signs of right ventricular hypertension; (4) dominant mitral stenosis is likely to be present, although the aortic valve may be either uninvolved, purely stenotic, purely insufficient, or a combination of both; (5) auscultation in the area along the lower left sternal edge will reveal principally or exclusively a presystolic murmur with sinus rhythm, or a mid-diastolic murmur with atrial fibrillation, each of which selectively increases with inspiration and decreases with expiration; auscultation of the second heart sound during active respiration generally will reveal absence of inspiratory splitting; (6) the electrocardiogram may reveal evidence of right atrial enlargement without right ventricular hypertrophy; and (7) a posteroanterior view of the chest may reveal only modest enlargement of the pulmonary artery segment in the presence of right atrial enlargement.

Summary

Clinical criteria for the recognition of tricuspid stenosis were studied in 13 cases, all personally observed by the authors. The results suggest that application of these criteria not only allows a confident diagnosis of tricuspid stenosis in a substantial majority of cases, but also allows the lesion to be recognized relatively early in its natural history.

Acknowledgment

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Addendum

Since this article was submitted for publication the authors have seen 2 more patients in whom tricuspid stenosis was diagnosed clinically and confirmed by cardiac catheterization. One patient, studied at Georgetown University Hospital, was a woman, age 42, with atrial fibrillation, coexisting mitral and aortic stenosis, and mild aortic regurgitation. The other case, studied at the National Heart Institute, was a woman, age 34, with sinus rhythm, coexisting mitral stenosis, and mild pure aortic regurgitation. The clinical and physiologic data in these additional cases were similar in all basic respects to the observations contained in this report.

Summario in Interlingua

Esseva studiate in 13 casos, omnes personalmente observate per le autores, le criterios clinic pro le recognition de stenosis tricuspidal. Le resultatos pare indicar que le application del criterios assi trovate permitte non solmente le establimento del diagnose de stenosis tricuspidal con alte grados de confidentia in un forte majoritate del casos sed etiam le recognition del lesion a un periodo relativemente precoce de su historia natural.

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The Dynamics of Rheumatic and Calcific Aortic Valve Disease

A Postmortem Study with the Use of the Pulse Duplicator

By RICHARD R. KELLEY, M.D., FAIRFIELD GOODALE, JR., M.D., AND BENJAMIN CASTLEMAN, M.D.

BECAUSE of recent advances in surgical technics, extracorporeal circulation, cardiac catheterization, and anesthesia, cardiac surgery has become established in many medical centers throughout the world. Since many operations on the heart involve plastic reconstruction of diseased valves, a more complete understanding is needed of their function under normal and pathologic circumstances. Most reports describing aortic stenosis and regurgitation have been based on gross observations of postmortem specimens examined by the usual pathologic technics.[1-6] Such an examination reveals little of the valvular function during life, and the pathologist can only roughly estimate the degree of stenosis and regurgitation.

A far better evaluation of diseased aortic valves can be made by a study of the heart post mortem on a pulse duplicator, which simulates valvular action under conditions resembling those existing during life. Work in this field was begun in 1952 by McMillan et al.,[7, 8] who perfused the ventricular chambers of hearts with a pulsatile flow and were able to photograph the aortic valve closing and opening under pressure created within the ventricle. In 1956 Davila et al.[9] developed a similar, but more elaborate machine. In 1955 Goodale and Shaw[10] in this laboratory measured pressure gradients across perfused valves to obtain a more accurate, quantitative functional evaluation. These studies were used by Austen, Shaw, Scannell, and Thurlbeck[11] as a basis for evaluating aortic valvulotomy. The present report describes a continuation of that work, with use of improved methods of studying valvular action and with measurements of simple pressure-flow relations across the heart valves.

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A large part of this work was carried out during 1957-1958, when Dr. Kelley was a Post-Sophomore Research Fellow in Pathology sponsored by the U. S. Public Health Service.

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Materials and Methods

During a period of 18 months 23 hearts with aortic valve disease due to rheumatic or calcific alterations were successfully perfused and studied on a pulse duplicator (figs. 1 and 2). Lucite cannulas were tied into the left atrium and proximal aorta of unopened hearts removed at autopsy. The coronary arteries were ligated at their origin, and the pericardium was removed. Water was perfused through one side of the heart by a centrifugal pump. A series of throttle valves allowed rapid change in the direction of flow to study regurgitation or stenosis without changing the cannula connections. Pressures on both sides of the valves were determined with water manometers. Intraventricular pressures were taken with small polyethylene catheters. The rate of flow was measured with a flow meter.

After pressure-flow relations were recorded, the movements of the valve were studied and photographed while the heart was perfused with a pulsatile flow. A solenoid-operated valve controlled by an electronic timer changed the steady flow of the centrifugal pump into a pulsatile flow. When the solenoid valve opened, water rushed past the aortic valve simulating the systolic ejection of blood. During diastole the flow of water was stopped and a second solenoid valve opened to relieve the pressure within the ventricle and allow the aortic valve to close. It was possible to vary the duration of both systole and diastole. After passing the aortic valve, the water was shunted through a simulated circulatory system, in which a variable valve created peripheral re-

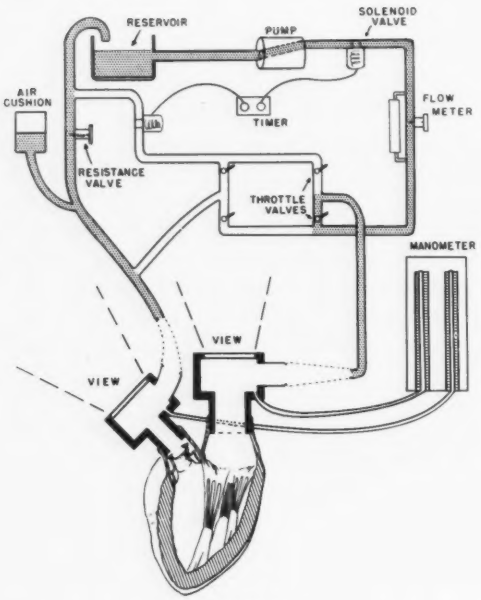

Figure 1

Diagram of the pulse duplicator used for study of the aortic valve. Throttle valves allow flow in either direction for observation of stenosis or regurgitation.

sistance and a variable air cushion provided an elastic recoil in diastole.

The valvular action was photographed through the clear lucite cannulas by means of an Exacta 35-mm. still camera with Panatomic X film and a Bolex 16-mm. reflex motion-picture camera with Kodachrome type-A film. Three American Optical Company microscope lights provided adequate, cool illumination, with the proper color balance.

Water was chosen as a perfusant instead of blood because of the obvious technical advantages. Unpublished work from this laboratory has shown that the difference in the pressure-flow relations between blood and water is not significant for the purpose of a study of this type.

Results

Valvular Hemodynamics

The orifice of the normal aortic valve opens to an area of 2.6 to 3.5 cm.^{2}, allowing a large amount of blood to pass without a significant pressure gradient between the aorta and the ventricle. When this orifice is narrowed by disease, the resistance to flow rises in proportion to the decrease in the size of the valve area. This phenomenon can be demonstrated graphically by plotting the pressure gradient across the valve against the flow past the orifice (fig. 3). A pressure gradient of greater than 10 cm. of water at a flow of 8 liters per minute documented stenosis in 19 of the 23 hearts. Fourteen of these were considered severely narrowed and created pressure gradients greater than 45 cm. of water; as would be expected, these patients had clinical evidence of aortic stenosis. Most of the patients with pressure gradients below 45 cm. of water had either pure aortic insufficiency or mild aortic stenosis without symptoms.

When the heart is perfused in a retrograde direction from the aorta, the normal aortic valve is uniformly competent to great pressures. In 13 of the 23 hearts there was measurable regurgitation. All but 2 of the 13 were associated with some stenosis. Six of the valves permitted reverse flows of greater than 2.8 liters per minute at a diastolic pressure of 100 cm. of water or less and were considered severely incompetent. As would be expected, those patients had clinical evidence of aortic insufficiency. In the 7 cases with reverse flows of less than 2.8 liters per minute the significance of the regurgitation could not be evaluated.

The perfusion data of representative cases of stenosis and regurgitation are plotted in figures 3 and 4.

Valvular Function

Normal Aortic Valve

The normal aortic valve opens freely when the pressure in the ventricle exceeds that in the aorta. The systolic rush of fluid pushes the leaflets apart, creating a triangular opening (fig. 5), and the leaflets often vibrate with the flow. In diastole (fig. 5), the cusps are immediately caught by a backward flow of blood as a reverse pressure gradient is established between the aorta and the ventricle, and the leaflets come together abruptly. The free edges of the valve cusps and a portion of the inferior cusp edge meet to form a seal 1 or 2 mm. in greatest thickness. This is an important means of sealing off the small fenestrations that often occur in the edge of the aortic and pulmonary valves, and the oppo-

ing surfaces enable each valve cusp to support the others and to withstand diastolic pressure gradients often in excess of 100 mm. Hg.

There is not infrequently a small area of incomplete closure of the aortic leaflets at the very center, apparently as the result of increase in the size of the normally small corpora arantii. The cause of this condition is not known, and its association with a diastolic murmur along the left sternal border is variable. Since the area of regurgitation is usually less than 1 mm. in greatest dimension, the perfusion data are not abnormal.

Rheumatic Aortic Valve Disease

An initial development in this condition is an acute inflammatory process of the rheumatic type that is especially marked at the lines of closure of the valves, where deposition of fibrin forms small vegetations. Eventually these areas undergo fibrosis, with consequent marked scarring and deformity of the valve. Calcification may ensue, leaving the valve immobile and often nearly functionless.

The following cases illustrate several patterns of deformity that result and the effect on the valvular function and hemodynamics.

Case 1, E. G. (A20,931). A 37-year-old woman was admitted to the hospital after treatment for 7 years for cardiac failure and pulmonary and peripheral emboli. The heart was enlarged to the anterior axillary line. A grade-II apical diastolic rumble, a grade-I diastolic blow along the left sternal border, and a grade-II systolic murmur in the pulmonic area were heard. A mitral valvuloplasty for stenosis was performed, but the patient died 4 months later because of a cerebral embolus.

At autopsy the mitral valve was still moderately stenotic, with marked fibrous scarring of the leaflets and the chordae tendineae. The aortic valve (fig. 6) showed minimal thickening of the leaflets, but it caused no detectable abnormality on perfusion.

Case 2, M. S. (A20,991). An 82-year-old woman gave no history of rheumatic fever and had no symptoms referable to the heart until 6 months before entry, when she noted the onset of orthopnea, exertional dyspnea, and ankle edema. The blood pressure was 240 systolic, 70 diastolic. The heart was enlarged to the anterior axillary line. Auscultation revealed a grade-III systolic murmur in the aortic area that was transmitted to the neck, a grade-II diastolic decrescendo murmur along the left sternal border, a grade-II pulmonic systolic murmur, and a grade-III apical systolic murmur that was transmitted poorly to the axilla. An electrocardiogram showed left ventricular hypertrophy. The patient died 2 months after entry because of severe congestive heart failure. The clinical diagnosis was calcific aortic stenosis with regurgitation.

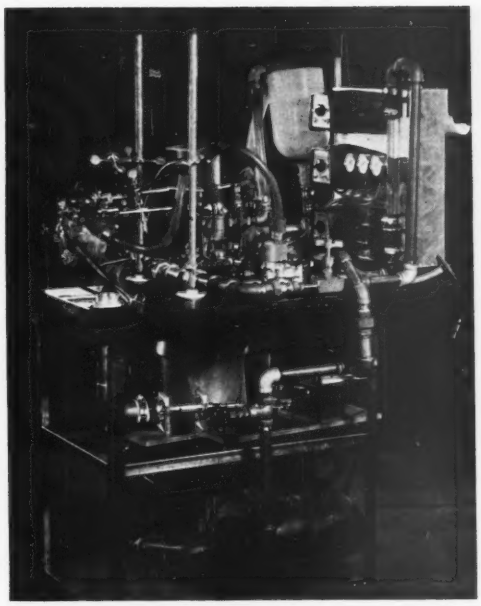

Figure 2

Photograph of the pulse duplicator. The heart is on the left side, the controls are on the right on the upper level, and the centrifugal pump and reservoir tank are on the lower level.

At autopsy the heart weighed 400 Gm. and all the valves were normal with the exception of the aortic valve (fig. 7). There was moderate scarring of this valve, with some fusion of the commissures, but it created no stenosis and only slight insufficiency (figs. 3 and 4). The latter finding could account for the diastolic murmur at the left sternal border, but does not fully explain the wide pulse pressure.

Case 3, L. S. (A20,598). A 55-year-old woman with known rheumatic heart disease was incapacitated by orthopnea, dyspnea on slight exertion, and anginal pains. Left heart catheterization revealed a large diastolic pressure gradient across the mitral valve and a left ventricular systolic pressure of 150 mm. Hg. The radial blood pressure was 120 mm. Hg. Auscultation revealed a grade-III apical systolic murmur that was transmitted to the axilla, a grade-III apical diastolic

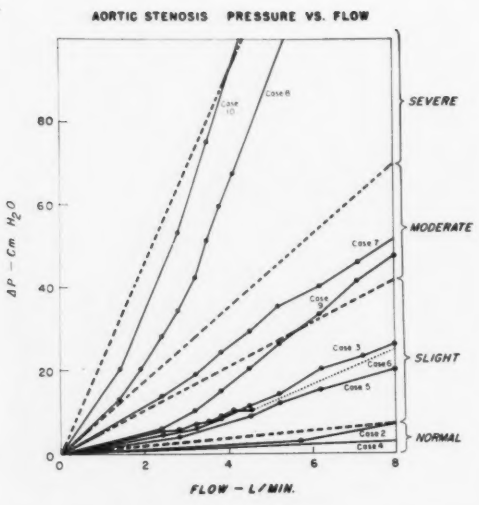

Figure 3

Pressure flow relations in aortic stenosis. The broken lines indicate approximate division between degrees of severity.

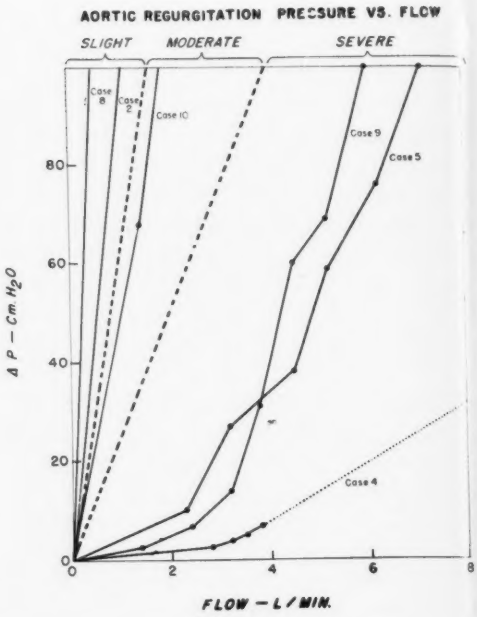

Figure 4

Pressure flow relations in aortic regurgitation. The broken lines indicate approximate division between degrees of severity. The unbroken lines indicate the data on specific cases.

murmur, a grade-III systolic murmur in the aortic area, and a grade-III diastolic murmur along the left sternal border in the third and fourth interspaces. She underwent mitral valvulotomy for relief of the mitral stenosis, but died in congestive heart failure 1 month later.

At autopsy tricuspid stenosis and mitral stenosis were found. The latter had been relieved by the operation. The aortic valve (fig. 8) demonstrated a more advanced stage of rheumatic scarring than in the previous cases. Fibrous and calcific infiltrations prevented complete opening, and a pressure gradient of 26 cm. of water developed at a continual systolic flow at 8 liters per minute (fig. 3). In diastole the valve closed quickly and completely, preventing regurgitation. The findings can account for the aortic systolic murmur, and it is possible that the left sternal border diastolic murmur arose in the mitral or pulmonic valves.

Case 4, A. B. (A20,937). Progressively severe rheumatoid arthritis had developed in a 46-year-old Negro man since the age of 16 years, and at 42 years he required digitalization because of progressive cardiac decompensation. The heart was enlarged to the left, with the apical beat in the midaxillary line. He had a grade-II systolic murmur in the aortic area that radiated to the neck, a grade-III diastolic murmur at the left sternal border, a grade-II apical systolic murmur and a vague mid-diastolic rumble at the apex. He died suddenly on the fourth hospital day. The clinical diagnosis was rheumatic heart disease, with aortic insufficiency and stenosis and questionable mitral stenosis.

At autopsy the mitral valve was scarred and the chordae tendineae were slightly thickened, but no stenosis or regurgitation could be demonstrated. The aortic valve was an example of marked valvular incompetence, without stenosis, due to scarring and irregular loss of substance at the leaflet margin (fig. 9).

Case 5, H. P. (A21,644). A 65-year-old man had an attack of acute rheumatic fever at the age of 33 years and cardiac symptoms developed 1 year before death. On admission he was in congestive heart failure. The heart was enlarged to the anterior axillary line. A grade-III harsh systolic murmur was heard in the aortic area and was transmitted up the carotid arteries and over the entire precordium. There was a grade-II diastolic murmur along the left sternal border. He died suddenly on the ninth hospital day.

At autopsy there was mild fibrous scarring of the mitral valve, but no stenosis or insufficiency. The aortic valve (fig. 10) showed slight stenosis with a pressure gradient of 18 cm. of water at

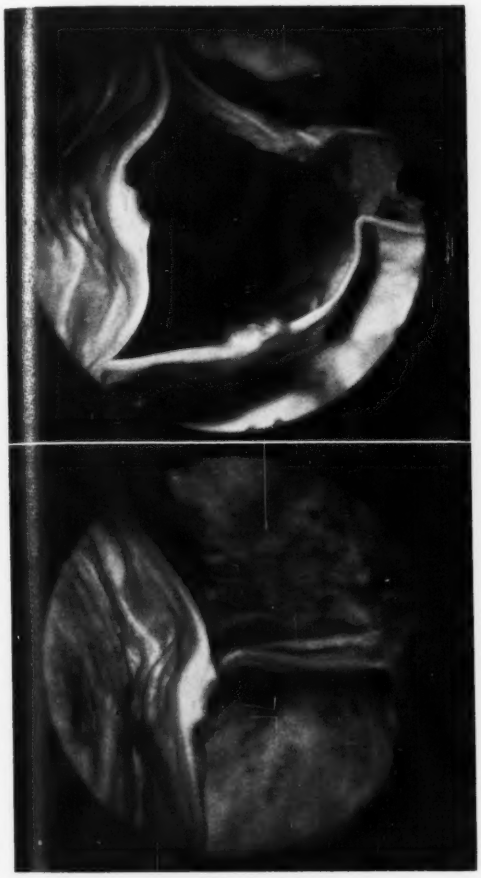

Figure 5

Normal aortic valve. Top, *systole;* bottom, *diastole.*

Figure 6

Case 1. Rheumatic heart disease. Top. *(Systole). There is minimal thickening of the valve leaflets, especially in the region of the corpora arantii, but adequate pliability remains for full opening.* Bottom. *(Diastole). There is a small area where the leaflets do not completely meet, which did not allow a significant amount of retrograde flow but may have been the cause of the diastolic murmur heard at the left sternal border.*

8 liters of continual flow, as well as severe regurgitation that permitted 7 liters of reverse flow per minute at a diastolic pressure of 100 cm. of water (figs. 3 and 4).

Calcific Aortic Valve Disease

In the following cases of aortic stenosis and regurgitation the patients did not present a definite history of rheumatic fever, and postmortem examination failed to demonstrate obvious indications of healed rheumatic activity, leaving the etiology of the lesion unsettled.

Case 6, A. F. (A20,824). A 68-year-old man had had hypertension for 16 years. His heart was slightly enlarged to the left, with a grade-II systolic murmur heard best at the base and in the aortic area. There was no diastolic murmur. At autopsy calcification of the mitral annulus was present. The other valves were normal except for the aortic valve, in which nodular calcific deposits at the base of the leaflets created a slight stenosis and minimal regurgitation (figs. 3 and 11).

Case 7, M. D. (A21,223). A 92-year-old man was found stuporous and paralyzed on the right side. The heart was enlarged to the anterior axillary line, and a grade-III blowing systolic

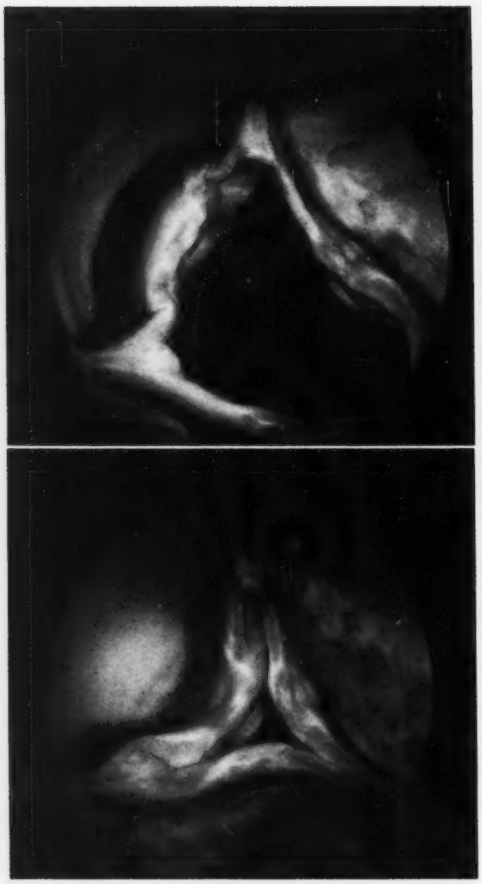

Figure 7

Case 2. Rheumatic heart disease. Top. *Moderate fibrous thickening of the leaflets and fusion of the commissures up to 4 mm. from the aortic wall restrict systolic opening, but not sufficiently to cause a significant pressure gradient.* Bottom. *In diastole, leaflet thickening and loss of marginal tissue create a central triangular area of insufficiency that permitted small amounts of retrograde flow and could account for the diastolic murmur at the left sternal border.*

murmur was heard over the entire precordium and maximally at the apex, with transmission into the neck. There was no diastolic murmur. He died suddenly on the eighth hospital day.

At autopsy the heart weighed 520 Gm. The mitral valve was slightly indurated by hard, yellow, calcific deposits on the ventricular surface of the leaflets, but it was not stenotic and the chordae tendineae were not thickened. The

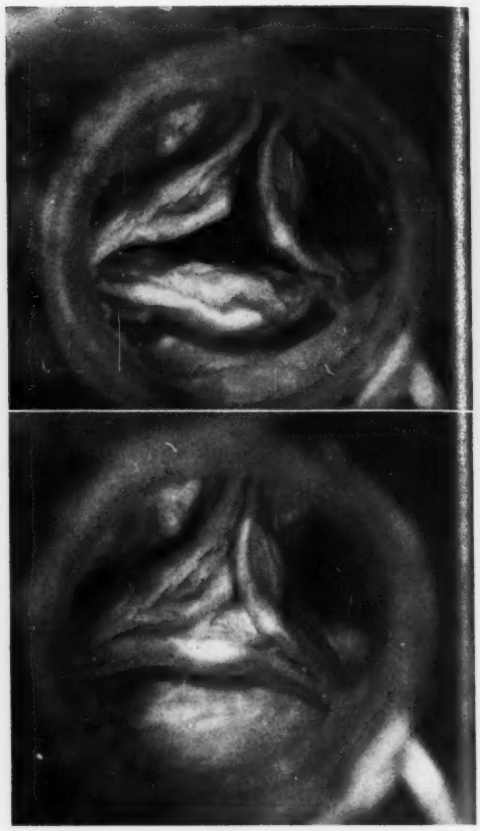

Figure 8

Case 3. Rheumatic heart disease with slight stenosis. Top. *A combination of fibrous thickening and diffuse calcific infiltration of the leaflets prevents complete opening.* Bottom. *There is enough residual pliability to allow closure in diastole.*

aortic valve (fig. 12) was moderately stenotic, with thickening of the leaflets by fibrous tissue and deposits of multiple nodules of calcium in the leaflet substance. These changes created a significant pressure gradient across the valve of 50 cm. of water at a flow of 8 liters per minute (fig. 3). A small area of regurgitation was created in the middle of the valve, where the thickened leaflets were unable to close completely.

Case 8, S. T. (A20,608). A 57-year-old man with metastatic carcinoma was admitted for terminal care. There was no history of rheumatic fever. The heart was enlarged, with a palpable thrill and a grade-IV systolic murmur heard best in the aortic area and transmitted to the neck and apex. The aortic second sound was absent.

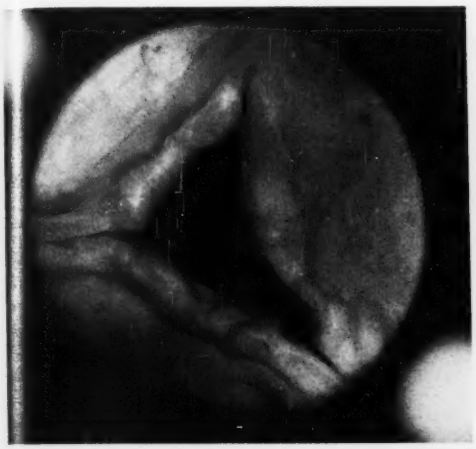

Figure 9

Case 4. Rheumatic heart disease with marked aortic regurgitation. Severe loss of tissue at the leaflet margins from scarring and rolling leaves a large patent area in diastole. Resistance to forward flow was normal and resistance to reverse flow was minimal.

The blood pressure was 98 systolic, 70 diastolic, and an electrocardiogram showed left ventricular hypertrophy.

At autopsy the heart weighed 600 Gm. The aortic valve showed marked fibrosis and thickening of the leaflets, in which multiple nodules of calcification were found (fig. 13). At a nonpulsatile flow of 4.5 liters per minute there was a pressure gradient of 73 cm. of water across the valve (fig. 3). In diastole the valve closed almost completely (fig. 4). The other valves were normal.

Case 9, W. J. (A21,053). A 47-year-old man had had progressive exertional dyspnea, anginal pains, and paroxysmal nocturnal dyspnea for 5 years. The blood pressure was 95 systolic, 85 diastolic, and the left border of the heart was percussed in the midaxillary line in the sixth interspace. A grade-II harsh basal systolic blow was transmitted to the neck and precordium, and a grade-II long, soft diastolic murmur was heard along the left sternal border.

At autopsy the heart weighed 760 Gm. All the valves were normal with the exception of the aortic valve (fig. 14), which was bicuspid, with marked fibrous and calcific thickening that created a moderate stenosis (gradient of 47 cm. of water at 7 liters) and a severe insufficiency (reverse flow of 5.6 liters per minute at a pressure of 100 cm. of water).

Case 10, A. M. (A21,393). A 48-year-old man

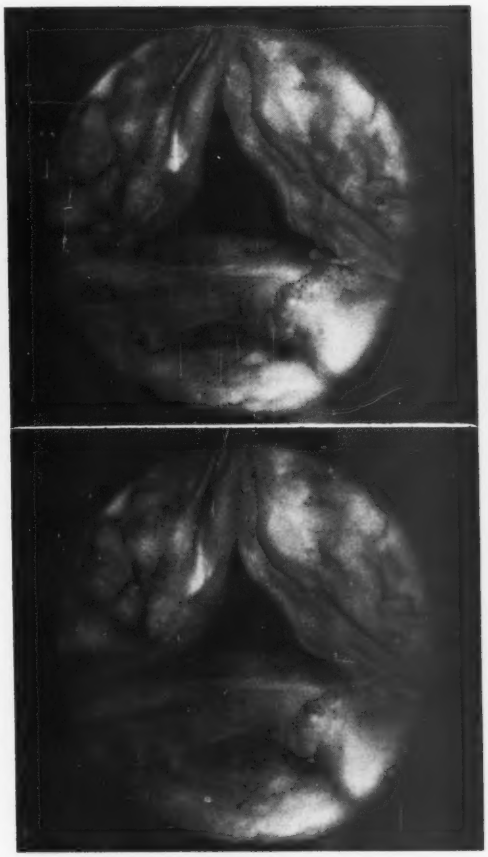

Figure 10

Case 5. Rheumatic heart disease with slight stenosis and severe regurgitation. Top. *The commissures are fused, and the cusps are thickened and distorted by fibrous tissue and nodules of calcific deposits, rendering the leaflets moderately rigid and limiting their separation, with a resultant slight stenosis.* Bottom. *During diastole, the nodules of calcific material prevent molding of the leaflets to complete closure.*

with no history of rheumatic fever, developed a systolic murmur 10 years before admission, a posterior myocardial infarction with typical electrocardiographic changes 6 years later, and episodes of dyspnea 1 year later. Physical examination revealed an enlarged heart with a diminished aortic second sound, a grade-III aortic systolic murmur that was transmitted to the neck, apex, and axilla, and a grade-I short diastolic blow at the left sternal border. The blood pressure was 110 systolic, 90 diastolic. Catheteriza-

Figure 11

Case 6. Calcific aortic valve disease with slight stenosis. Top. *There is slight fibrous thickening and deposition of multiple nodules of calcific material, mainly at the base of the cusps. During systole a large stellate area is created that permits a moderate flow, with only slight resistance.* Bottom. *In diastole the rigid leaflets fail to meet in a small area in the center.*

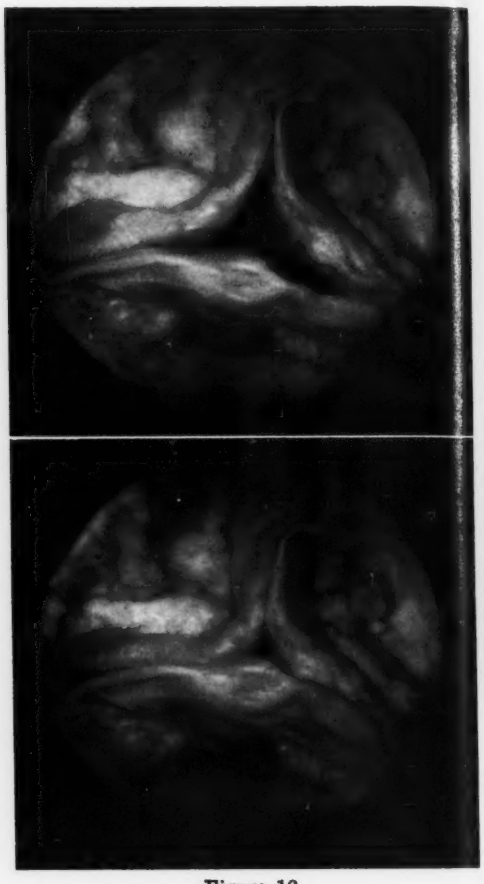

Figure 12

Case 7. Calcific aortic valve disease with moderate stenosis. Top. *Confluent nodules of calcific material deposited mainly in the base of the leaflets and fibrous thickening restrict opening during systole.* Bottom. *There is still adequate flexibility and substance at the free margin of each leaflet to allow almost complete closure of the valve during diastole.*

tion of the left side of the heart showed a gradient of 122 mm. Hg during systole across the aortic valve and a left ventricular pressure of 28 during diastole. The cardiac output was not measured. He died 3 days later of pulmonary emboli.

At autopsy the heart weighed 700 Gm. The aortic valve (fig. 15) was bicuspid. Both leaflets were firmly fixed by massive nodules of calcific material, creating a small, rigid, nonmovable orifice that was severely stenotic (forward pressure gradient of 100 cm. of water at 4.2 liters per minute flow) and moderately incompetent (reverse flow of 1.8 liters per minute at a diastolic pressure of 100 cm. of water). The other valves were normal.

Discussion

To function normally the aortic valve must prevent blood from flowing in a retrograde direction during a period of decreased pressure in the ventricle, without creating a sig-

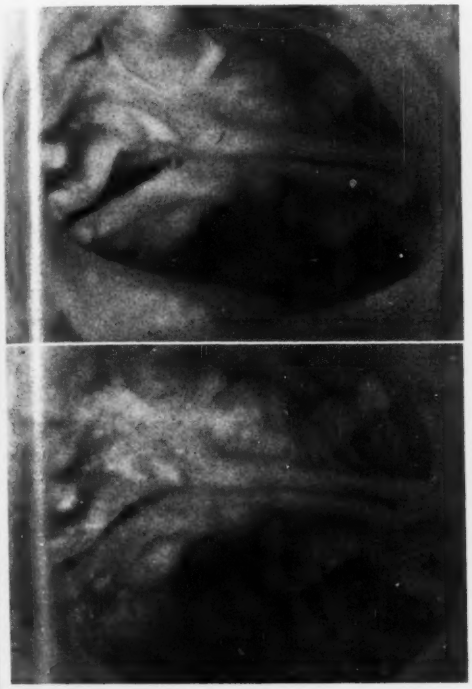

Figure 13

Case 8. Calcific aortic valve disease with severe stenosis. Top. *Multiple confluent nodules of calcific deposits, fibrous thickening and extensive fusion of the commissures of 2 cusps result in a slit-like opening in systole.* Bottom. *There is enough residual flexibility in half of one leaflet to permit closure in diastole with minimal regurgitation.*

nificant resistance to forward flow. With the pulse duplicator one can document the degree to which this action is accomplished by recording the hemodynamic characteristics of the valve and by studying the leaflet action in systole and diastole. Pressure-flow studies are important because they delineate degrees of stenosis and regurgitation far more accurately than is possible with the opened heart or a heart examined without fluid pressure on the valve.

The data compiled from these studies confirm that the aortic valve can be narrowed considerably, even to the point of creating some resistance to flow, without producing significant cardiac symptoms. Likewise, a cer-

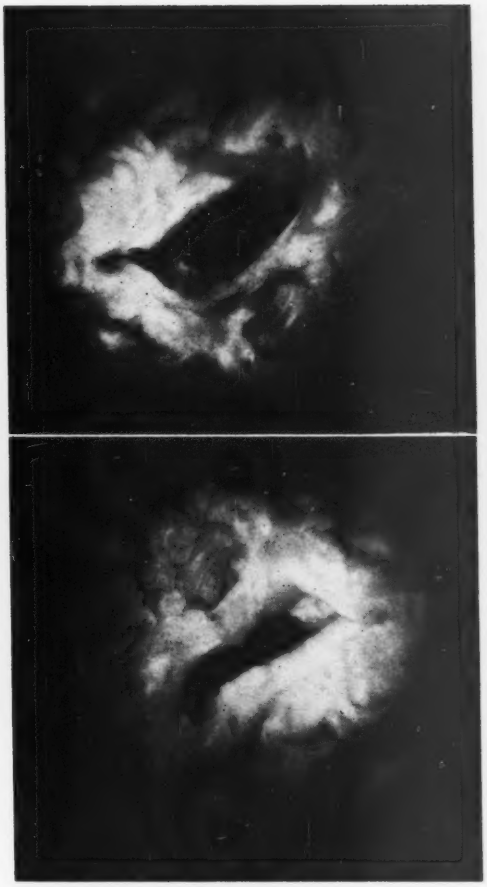

Figure 14

Case 9. Calcific aortic valve disease with moderate stenosis and severe regurgitation. Top. *Extensive amounts of calcific material have created an almost immobile valve, with complete obliteration of one commissure.* Bottom. *A large nodule separates two of the leaflets on the left side and prevents complete closure during diastole.*

tain amount of aortic insufficiency can be tolerated without ill effects. The number of cases in this series is inadequate for accurate definition of the degrees of stenosis and regurgitation that produce clinical signs and symptoms. The findings suggest, however, that a heart can compensate adequately for a stenosis that produces a pressure gradient of around 40 cm. of water when perfused postmortem with a nonpulsatile flow of 8 liters per

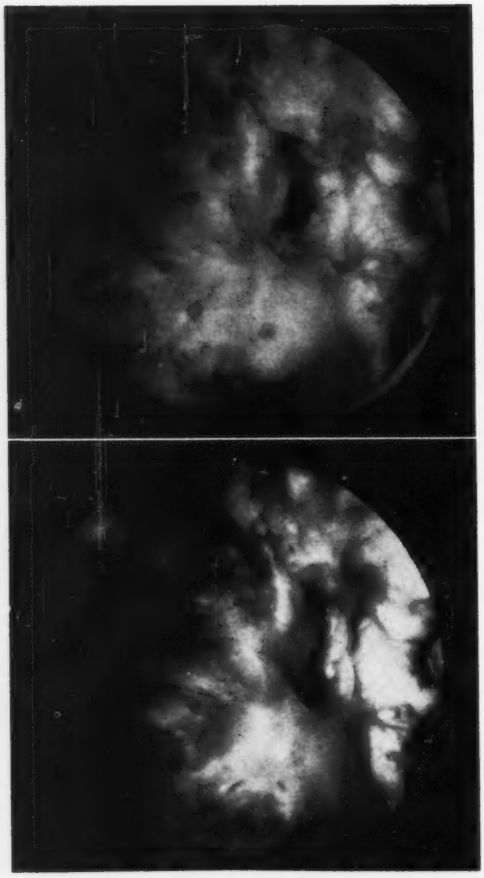

Figure 15

Case 10. Calcific aortic valve disease with severe stenosis and moderate regurgitation. Top. *Massive amounts of calcific material have created a rigid, nonmovable orifice. Two commissures are completely obliterated, and the third is reduced to a thin slit seen at the top of the photograph.* Bottom. *During diastole there is little change in the orifice, allowing moderate regurgitation.*

minute. The presence of an area of incomplete closure that allows a reverse flow greater than 2.8 to 4 liters per minute at a pressure of 100 cm. of water probably is also significant clinically. More exact data of this nature are needed as an aid to cardiac surgery because although a deformed valve cannot be completely restored to normal function in many cases, stenosis or regurgitation can be decreased to a level that may be tolerated without significant symptoms.[11, 12]

The graphs of pressure versus flow for a stenotic aortic valve do not follow the usual exponential curve plotted for flow past a standard circular orifice of an equivalent area. This circumstance probably is a result of at least two factors: the valve orifice is very irregular, creating a unique hemodynamic situation; and in this experimental situation in which continual flow is used, each increment of flow forces open the rigid, diseased valve slightly, creating successively larger areas in some cases.

The cases presented illustrate 3 important alterations in an aortic valve that often occur concomitantly, although any one alteration may predominate.

1. Fusion of the commissures: In most cases of severe aortic stenosis seen in this laboratory, fusion of the leaflets at their commissures has been a significant finding, and indeed often the predominating lesion in patients with a history of rheumatic heart disease.

2. Thickening of the cusps: Fibrous and calcific infiltration in the cusps is often as important an alteration as fusion of the commissures. The firmness and bulk of the calcific nodules within the cusps prevent them from separating widely enough to create a functionally normal orifice, with resultant stenosis and sometimes valvular insufficiency. In the normal aortic valve (fig. 5) the soft and pliable leaflets mold to fit one another during diastole. When the leaflets are rigid, the opposing surfaces cannot mold and complete valve closure is impossible (fig. 10), as if 3 rigid semicircles were used to occlude an area without change of shape or overlapping. Large calcific nodules deposited between the leaflets may further contribute to insufficiency by wedging the leaflets apart (fig. 14) or by fixing the valve in a rigid, partially opened position in which it moves only slightly in a pulsatile flow (fig. 15).

3. Retraction of the leaflet margin: A third important change in the aortic valve is loss of leaflet substance because of scarring at the

leaflet margin. This can be the predominant lesion (fig. 9) or can accentuate the insufficiency present due to calcification and fusion of the commissures (fig. 10). The scarring process at the valve margin is usually irregular and in minimal amounts can also contribute to the creation of a small regurgitant area that results only in a diastolic murmur (fig. 6).

Therefore, fusion of the commissures, calcification of the leaflets, and loss of leaflet substance at the margins may all occur in the same valve to some degree. The type of lesion that results depends on which change predominates and how the changes interrelate to compound the functional alteration. These facts assume particular importance when surgical reconstruction of a diseased aortic valve is contemplated because more than one type of lesion may require correction for a functionally beneficial result.

Summary and Conclusions

Improved methods of studying the aortic valve post mortem are presented.

Ten cases illustrate the major alterations seen in rheumatic and calcific aortic valve disease.

Fusion of the commissures, calcification of the leaflets, and loss of leaflet substance at the margins all contribute to aortic stenosis and insufficiency. The functional result is restriction of movement of the leaflets so that they do not fully attain the normal position in systole and diastole. Although any one change may predominate, generally all three contribute to the functional abnormality.

Such valvular studies should be of particular value to the surgeon by providing a working model on which to practice technics and to develop new methods of approaching the problem of aortic valve disease. They also provide an objective measure of operative results.

Summario in Interlingua

Es presentate meliorate methodos pro le studio del valvula aortic post morte.

Dece casos es usate pro illustrar le major alterationes vidite in morbo rheumatic e calcific del valvula aortic.

Fusion del commissuras, calcification del cuspides, e perdita de substantia in le cuspides in le area marginal, omne istos es factores contribuente al disveloppamento de stenosis e insufficientia aortic. Le resultato functional es restriction de movimento pro le cuspides de maniera que illos non attinge le position plenmente normal in systole e in diastole. Ben que le un o le altere del mentionate vitiationes pote predominar, generalmente omne le tres contribue al anormalitate functional

Tal studios valvular deberea esser de valor particular pro le chirurgo qui trova in illos un modello permittente exercitios de technica e providente le opportunitate de disveloppar nove methodos pro attaccar le problema de morbo del valvula aortic. Illos etiam offere le possibilitate de mesurar objectivemente le resultatos del intervention chirurgic.

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"Primary" Pulmonary Hypertension with Coexisting Portal Hypertension

A Retrospective Study of Six Cases

By RICHARD L. NAEYE, M.D.

THE PATHOGENESIS of the syndrome "primary" pulmonary arterial hypertension has been the subject of increasing interest in recent years.[1-12] The syndrome is characterized by pulmonary arterial hypertension in the absence of significant primary pulmonary parenchymatous disease or primary cardiac disorder. The hypertension has usually been attributed to pulmonary vascular lesions, which increase the resistance to blood flow through the lesser circulation. In most cases the most striking vascular change has been proliferation of endothelial cells and fibrous tissue in the intima of small pulmonary arteries. In a few individuals pulmonary arterial thrombi have been numerous, suggesting that the sclerotic process may have been the consequence of recurrent emboli.[1-5] In many other cases the most prominent vascular alteration has been an acute or healing arteritis.[1, 6, 10-12] In some of these instances it has been difficult to determine whether the arteritis preceded the hypertension or was its consequence.[6, 13] In any case, the final sclerotic lesions give few indications of their origin, the healed lesions of arteritis often being indistinguishable from those that follow embolism or other forms of trauma to the pulmonary arteries.[14, 16] The syndrome of "primary" pulmonary hypertension may well have a diverse etiology.

"Primary" pulmonary hypertension has rarely been related to other disorders. Only 3 examples of an association between "primary" pulmonary arterial hypertension and portal venous hypertension have been reported.[17-19] In one, recurrent pulmonary emboli arose from a spontaneously developing portocaval shunt in a patient with portal hypertension.[17] In another, multiple pulmonary arteriovenous fistulas were discovered in an individual with juvenile cirrhosis.[18] In the third, pulmonary hypertension was unexplained.[19] The current study deals with pulmonary and portal vascular changes in 6 patients who had evidence of both pulmonary and portal hypertension. Anatomic findings suggest that the association of these 2 types of hypertension may have been more than coincidental.

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Methods

Cases of coexisting portal and pulmonary hypertension were selected in which there was no evidence of significant primary pulmonary or cardiac disease. Studies were undertaken of the pulmonary and portal vessels. Tissue blocks from all lobes of the lungs were serially sectioned and stained with Verhoeff and Van Gieson stains. In 1 case (no. 6) the pulmonary arteries were injected with a colored gelatin preparation. In each case the portal vein and as many of its collateral channels as possible were studied by multiple sections.

Subjects

Case 1

This 42-year-old man (DH 183265) was admitted with right chest pain and hemoptysis. He had felt "rundown" for several years and had several episodes of pleuritic type pain, the last a year before death. The day before admission he developed pleuritic chest pain accompanied by weakness, chills, and anorexia.

On admission he was dyspneic and debilitated, and had a fever of 101 F. Breath sounds were diminished and a pleural rub was noted in the right lower chest. The neck veins were distended. Heart sounds were normal. The heart was enlarged by x-ray and a dense pneumonic infiltrate filled the lower lobe of the right lung. The liver appeared enlarged. Pneumococci were common in a sputum culture. Electrocardiogram showed incomplete right bundle-branch block, and right ventricular hypertrophy. The hemoglobin was 14.7 Gm. per cent and the white blood cell count was 16,000, with 18

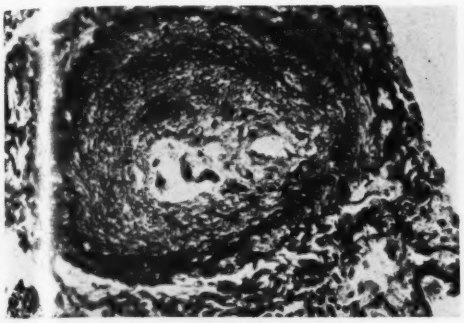

Figure 1

Case 1. Intimal proliferation of endothelial cells and fibroblasts in a pulmonary muscular artery. Elastic-tissue stain.

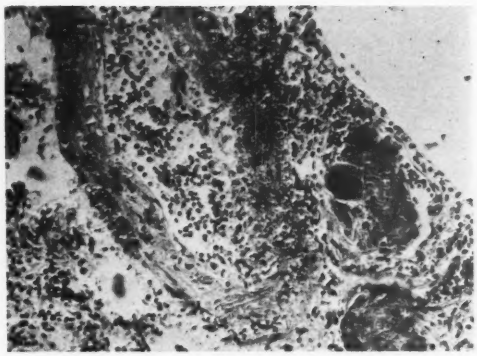

Figure 2

Case 2. Fibrinoid necrosis and granulation in the wall of a pulmonary muscular artery. A branch of the artery to the right is thrombosed. Hematoxylin and eosin stain.

per cent nonsegmented neutrophils. The serum bilirubin was 8 mg. per cent, and the urine was positive for bilirubin. A cephalin flocculation test was 4+. The patient became progressively weaker after admission and died on the fifth day. The clinical impression was lobular pneumonia with possible pulmonary infarcts.

At autopsy the patient was icteric. The right pleural cavity contained 300 ml. of turbid fluid. The enlarged heart weighed 490 Gm. The right atrium and ventricle were dilated. The hypertrophied right ventricle measured 6 mm. in thickness. Other cardiac measurements were reported to be normal. The lungs were edematous, and an acute lobular pneumonia was located in the right middle lobe. Gross arterial emboli and infarcts were absent. The enlarged, nodular liver weighed 1,570 Gm. Microscopically there was severe hepatic portal cirrhosis. The portal vein was markedly narrowed over much of its extrahepatic length by old and recent thrombi. The congested spleen weighed 750 Gm. Esophageal and gastric venous varices were prominent. No thrombi were found in pelvic or leg veins.

Pulmonary vascular changes were extensive in all lobes. Atheromata were present in the elastic arteries. Medial smooth muscle was hypertrophied in muscular arteries of all sizes. Emboli or thrombi in varying stages of organization were lodged in many of these muscular arteries. The lumina of many muscular arteries were markedly narrowed by intimal proliferation of endothelial cells and fibroblasts (fig. 1). In some cases only a tiny channel remained. Fibrinoid necrosis and granulation tissue were present in the walls of a few arteries (fig. 2). In some areas, segments of the muscular arteries had undergone a fusiform swelling. Their lumina and walls were replaced by fibrous tissue through which passed many tiny vascular channels (fig. 3). The tiny channels eventually emptied into one or more dilated branches of the muscular arterial system distally. The media of these distal arteries was often atrophic. These distal vessels often clustered about the artery of origin before passing into the pulmonary parenchyma to form normal pulmonary arterioles and capillaries. These plexiform-like lesions were found in many stages of development. Some were found at the point where arteries branched. Dilated veins were found in fibrous pleural adhesions.

Comment

Portal cirrhosis with old and recent thrombotic occlusions of the portal veins were associated with clinical and necropsy evidences of pulmonary hypertension, i.e., electrocardiographic changes, dilatation and hypertrophy of right ventricle, and many changes in small pulmonary arteries: smooth muscle hypertrophy, advanced intimal proliferative lesions, and many organizing thrombi.

Case 2

Five years before death this 28-year-old woman (PH 1382810) had an episode of anorexia and malaise, which followed "exposure" to infectious hepatitis. A year later the serum albumin was 2.7 Gm. per cent and the globulin 7 Gm. per cent. Two years before death her liver was enlarged and she was icteric. A cephalin flocculation test was 4+ and bromsulphalein retention 23 per cent at 30 minutes. She received corticosteroids and was well until 2½ months before death, when headaches and purpura developed. Hematemesis followed a month later. Massive ascites, icterus, and an enlarged liver and spleen were noted. Hematemeses continued and she lapsed into coma. She died after sudden car-

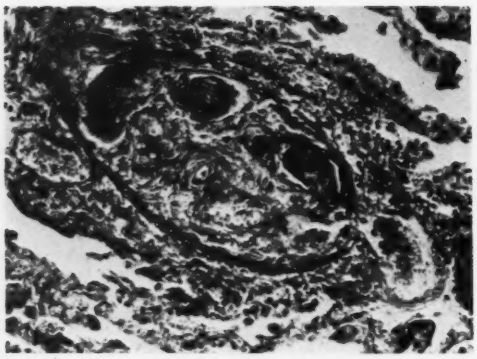

Figure 3

Case 1. An advanced plexiform lesion in a muscular pulmonary artery. Several of the channels are thrombosed. Elastic-tissue stain.

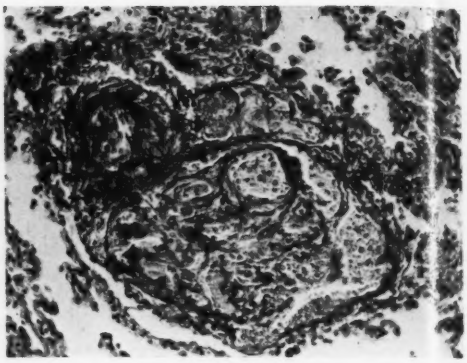

Figure 4

Case 2. A pulmonary muscular artery is transformed into a plexiform structure. The segment of artery just proximal to the lesion can be seen just above and to the left. Elastic-tissue stain.

diac arrest during an attempt to ligate bleeding esophageal varices. She had no alcoholic intake or known episodes of malnutrition. She had no evidences of cardiac or pulmonary disease during life. The clinical impression was advanced postnecrotic cirrhosis of the liver with portal venous hypertension and hemorrhage from esophageal varices. Death was attributed to cholemia.

Three liters of ascitic fluid were present at autopsy. The heart weighed 375 Gm. The right ventricular cavity was dilated and its wall was hypertrophied, varying in thickness from 0.4 to 0.5 cm. Other measurements included left ventricle 1.2 cm., tricuspid valve circumference 13.0 cm., mitral valve 10.0 cm., pulmonic 8.0 cm., and aortic valve 6.5 cm. The foramen ovale was closed. No abnormality was found on cross section of the lungs. Gross arterial thrombi were absent. The spleen weighed 650 Gm. due to chronic congestion. The irregularly nodular liver weighed 1,375 Gm. Microscopic examination supported the diagnosis of postnecrotic cirrhosis. An organizing thrombus occluded the portal vein in the porta hepatis. Large esophageal varices were ulcerated just below a Sensteken balloon. Organizing thrombi were present in varicose veins of both esophagus and stomach. Fresh blood filled the intestinal tract. No thrombi were found in pelvic or leg veins.

Vascular changes were extensive in the lungs. Emboli or thrombi were found in muscular arteries of many sizes. Advanced intimal proliferative lesions like those in case 1 were found in elastic arteries, muscular arteries, and in some arterioles. These had progressed to the plexiform stage in some arteries (fig. 4). Medial smooth muscle hypertrophy was found in most of the muscular arteries and in many of the arterioles. The walls of a few muscular arteries were necrotic.

Comment

Postnecrotic hepatic cirrhosis with thrombotic occlusion of the portal vein and many evidences of portal hypertension were associated with morphologic evidences of pulmonary hypertension, i.e., dilatation and hypertrophy of the right ventricle, medial muscle hypertrophy in pulmonary arteries and arterioles, advanced, intimal proliferative lesions in the pulmonary arterial bed, and organizing thrombi in pulmonary arteries.

Case 3

This 34-year-old man (PH 85086) had 170 hospital admissions during which he received 97,650 ml. of whole blood for thalassemia major. Despite splenectomy at age 5 years, his hemoglobin level could not be maintained above 7 Gm. per 100 ml. In the 2 years before death he developed diabetes mellitus and repeated bouts of cough, dyspena, chest pain, and fever. Hepatomegaly and ascites appeared. The terminal admission was for abdominal pain. He was icteric, and his heart was enlarged. Neck veins were distended, and the second pulmonic sound was louder than the second aortic sound. Ankle edema was present. The hematocrit level was 23 per cent and the leukocyte count was 13,550, with 20 normoblasts per 100 white cells. Target cells were common. The fasting blood sugar was 230 mg. per cent, blood urea nitrogen 58 mg. per cent, serum alkaline phosphatase 15.4 Bodansky units, and thymol turbidity 3+. An electrocardiogram revealed partial right bundle-branch block. On x-ray the large intestine was found to be dilated. He became stuporous and died on the third hospital day. The clinical impression was thalassemia major, severe hemosiderosis of the liver, pancreas, and other organs, diabetes mellitus, and partial obstruction of the large intestine.

At autopsy 3,000 ml. of ascitic fluid were present. The enlarged heart weighed 450 Gm. The right atrium and ventricle were dilated. Cardiac measurements were: right ventricular thickness 0.8 cm., left ventricle 1.8 cm., circumference tricuspid valve 13 cm., mitral valve 10 cm., pulmonic valve 8 cm., aortic valve 7 cm. Cross section of the lungs revealed atelectasis of the lower lobes. Gross vascular thrombi were absent. The brownish, finely nodular liver weighed 3,600 Gm. Microscopic examination confirmed the presence of a portal-type cirrhosis with heavy iron deposits. Hemosiderosis was severe in all of the viscera. The large bowel was obstructed by fibrous adhesions. No thrombi were found in the portal vein, or in the leg or pelvic veins.

Microscopic emboli or thrombi of varying ages were found in a number of pulmonary muscular arteries (fig. 5). Other pulmonary vascular changes were advanced. Atheromatous plaques were found in the elastic arteries. Arterial smooth muscle hypertrophy was like that found in the previous cases. Pulmonary arterioles often had a muscular coat. Intimal proliferation of endothelial cells and fibrous tissue was present in muscular arteries of all sizes and was most advanced in the smaller vessels. These proliferative lesions had progressed to the plexiform stage in a number of muscular arteries (fig. 6). As in other cases, thrombi were sometimes found in the small channels of these structures. The internal elastic membranes of muscular arteries were often found to be reduplicated.

Comment

Hepatic portal cirrhosis and portal venous hypertension were present in a patient with thalassemia major who had severe transfusion hemosiderosis. Morphologic evidences of pulmonary hypertension resembled those in cases 1 and 2.

Case 4

This 76-year-old woman (MFH A56-193) had evidence of cardiac decompensation for many years. She had no known history of hepatic or pulmonary disease. Terminal admission was for sharp pain in the left abdomen. She was cyanotic, dehydrated, and dyspneic. The blood pressure was 120/80 mm. Hg, her usual pressure having been 160/80 mm. Her heart was enlarged to percussion, and pulmonary rales were detected bilaterally. The hemoglobin was 13.1 Gm. per 100 ml. and the leukocyte count 26,000, with 23 per cent nonsegmented neutrophils. Urinalysis showed many leukocytes and erythrocytes. The blood urea nitrogen was 55 mg. per cent. The temperature on the third day rose to 104 F. and persisted. Then blood pressure gradually fell, and she died on the fifth day. Other clinical and laboratory data are lacking. The clinical impression was arteriosclerotic heart disease and acute pyelonephritis.

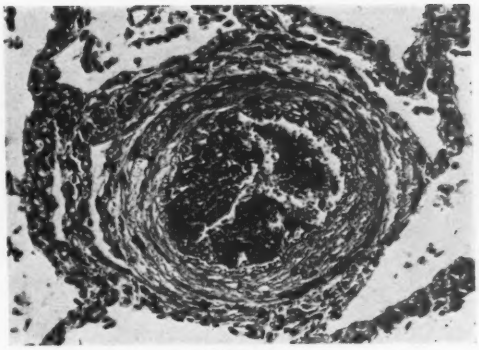

Figure 5

Case 3. Thrombus with early organization in the lumen of a pulmonary muscular artery. Hematoxylin and eosin stain.

At autopsy, the heart was noted to be enlarged but its weight was not recorded. The hypertrophied right ventricle measured 0.6 cm. in thickness and the left ventricle, also somewhat hypertrophied, 1.6 cm. All of the cardiac chambers were dilated. The tricuspid valve measured 14 cm. in circumference, the mitral 9.5 cm., the pulmonic 9.0 cm., and the aortic 7.0 cm. Arteriosclerosis of the coronary arteries was minimal. Both lungs were edematous and had areas of atelectasis. Gross arterial thrombi were absent. The nodular liver weighed 1,550 Gm. Gross and microscopic study revealed an advanced portal cirrhosis. Collateral venous channels in the stomach and esophagus were dilated but available sections contained no thrombi. The enlarged spleen, which weighed 620 Gm., had small foci of parenchymal necrosis. Both kidneys had severe, acute pyelonephritis. No thrombi were found in pelvic or leg veins.

Many vascular abnormalities were present in the lungs, which help to explain the cor pulmonale. Atheromata were found in the elastic arteries. Medial smooth muscle was hypertrophied in muscular arteries and in arterioles. In a few instances, walls of muscular arteries showed fibrinoid necrosis. The most striking changes were found in the intima of these vessels. Proliferative changes narrowed their lumina so markedly that in some instances the channels were almost obliterated. In a few vessels, these proliferative changes had progressed to the plexiform stage. The plexiform lesions were found in straight as well as in branching segments of the muscular arteries. Thrombi or emboli were present in many muscular arteries.

Comment

This patient had portal cirrhosis of undetermined cause with portal hypertension. Morphologic evidences of pulmonary arterial hypertension were like those found in cases 1, 2, and 3.

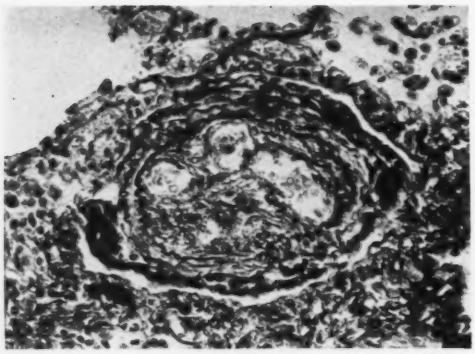

Figure 6

Case 3. A plexiform lesion in a muscular pulmonary artery. Elastic-tissue stain.

Case 5

This 76-year-old man (MFH A57-247) developed cardiac failure 4 years before death and did well on digitalis. He had no known history of hepatic or pulmonary disease. Nine months before death a transient episode of intestinal obstruction developed due to an incarcerated intestinal loop in a large umbilical hernia. Subsequently, his cardiac failure was difficult to control. The terminal admission was for recurrent intestinal obstruction. The hernia could not be reduced. The hemoglobin was 13.9 Gm. per cent. He had progressive cardiac failure and died on the thirteenth hospital day without operation. Other clinical and laboratory data are lacking. The clinical impression was intestinal obstruction due to intestine incarcerated in umbilical hernia, and arteriosclerotic heart disease.

At autopsy the umbilical hernia contained 2 loops of ileum, one of which was gangrenous. The lower extremities were edematous and 200 ml. of ascitic fluid were present. The heart weighed 660 Gm. The hypertrophied right ventricle was 0.8 cm. in thickness, the left ventricle 1.0 cm. The tricuspid valve measured 14 cm. in circumference, the mitral 12 cm., the pulmonic 10 cm., and the aortic 8 cm. Coronary arteriosclerosis was almost absent. The lungs were edematous and had foci of acute lobular pneumonia. Gross thrombi were absent. The spleen weighed 280 Gm. and showed evidence of chronic congestion. The finely nodular cirrhotic liver weighed 1,800 Gm. The cirrhosis was portal in type and moderately severe. Esophageal varices were large but free from thrombi. No thrombi were found in the portal vein. No other source of emboli was found.

Pulmonary vascular changes were extensive. Atheromata were present in the large elastic arteries. Medial muscular hypertrophy was prominent in muscular arteries and arterioles. Thrombi or emboli in varying stages of organization were found in scattered muscular arteries. Muscular arteries of all sizes showed an advanced intimal proliferation of endothelial cells and fibroblasts like that found in other cases. In some instances, previously large lumina were reduced almost to capillary size.

Comment

Portal cirrhosis with portal hypertension were associated with morphologic evidences of pulmonary hypertension resembling those found in the previous 4 cases.

Case 6

This 13-year-old schoolgirl (PH 123417) had numerous hospital admissions for bleeding esophageal varices. A sudden hematemesis at age 12 required transfusions. Additional episodes appeared during succeeding years. At age 5, esophageal varices were demonstrated by x-ray. The spleen was enlarged, but the liver was not. Liver function tests were normal except for 2+ cephalin flocculation and thymol turbidity. At laparotomy the portal vein was not found but many extrahepatic collateral channels of this vessel were located. A spleno-renal shunt was performed, splenic venous pressure decreasing from 340 to 275 mm. of water. At age 11 she had her only other hematemesis until her final illness. The terminal episode began with melena. On admission she was weak and pale with a hematocrit level of 23 per cent. The leukocyte count was 9,900, with a normal differential count. The prothrombin time was 16 seconds (normal, 13 seconds), serum bilirubin 1 mg. per cent, bromsulphalein retention at 30 minutes 24 per cent, alkaline phosphatase 10.5 King-Armstrong units, and serum protein pattern was normal. A Coombs test was positive. She had a systolic murmur in the third left interspace. An electrocardiogram was suggestive of right ventricular hypertrophy. Cardiac fluoroscopy and esophagram demonstrated esophageal varices, cardiac border with right ventricular configuration, and dilated pulmonary artery. After a partial esophageal-gastrectomy with jejunal interposition her temperature remained elevated. On the sixth postoperative day she died following an episode of sudden chest pain and dyspnea. The clinical impression was cavernous transformation of the portal vein, severe portal hypertension with hemorrhage from esophageal varices, and pulmonary arterial hypertension of undetermined cause.

Large pleural effusions were present at autopsy. The enlarged heart weighed 380 Gm. The right atrium and ventricle were dilated. The hypertrophied right ventricular wall measured 0.7 cm. in thickness, the left ventricular wall 1.5 cm. The

circumference of the tricuspid valve was 11 cm., the mitral 9 cm., the pulmonic 6 cm., and the aortic valve 5 cm. The pulmonary artery was dilated. No congenital cardiac malformation was found. The spleno-renal anastomosis was patent. A thrombus occluded the portal vein just beyond the junction of splenic and superior mesenteric veins. In the porta hepatis the portal vein was partially recanalized. The liver weighed 1,370 Gm. and was morphologically normal except for centrolobular congestion. The segment of jejunum interposed in the esophagus was intact. Large varices in the proximal esophagus had no thrombi. Cross section of the lungs revealed atelectasis of the lower left lobe. Gross thrombi were absent. Pelvic and leg veins were free from thrombi.

Pulmonary vascular changes were severe but in some respects were different from those found in other cases. A severe necrotizing arteritis was found in muscular arteries from all areas (fig. 7). This usually involved the entire vessel wall and was often associated with an organizing thrombus. These necrotic changes were far more severe than those found in other cases. Other vascular changes included medial muscle hypertrophy in muscular arteries and arterioles. Intimal proliferation of endothelial cells and fibroblasts was found in most muscular arteries (fig. 8). In some instances this process completely occluded arterial lumina. There was often reduplication of the internal elastic membrane in these arteries. Atheromata were present in the intima of elastic arteries. Bronchial arteries and veins were structurally normal. In one lung, pulmonary arteries were injected with a gelatin preparation. This did not penetrate arteries smaller than 20 μ in luminal diameter. None reached the pulmonary veins or bronchial vessels.

Comment

Old and recent thrombosis of the portal vein with severe portal hypertension was found. Many clinical and morphologic features of pulmonary hypertension resemble those found in the previous cases. The severe, necrotizing pulmonary arteritis found in this case was more severe than that present in the other 5 cases.

Discussion

Six cases are described in which portal venous hypertension coexisted with "primary" pulmonary arterial hypertension. The pulmonary hypertension was suggested in all cases by the postmortem findings of right ventricular hypertrophy and dilatation. Additional evidence for hypertension in these individuals was the demonstration of advanced lesions in the pulmonary arteries. In several of the

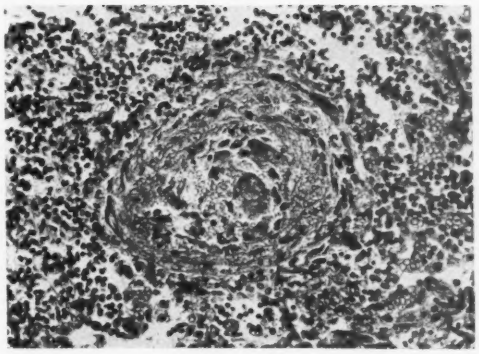

Figure 7

Case 6. Severe necrotizing arteritis in a pulmonary muscular artery. An organizing thrombus is noted in the lumen. Hematoxylin and eosin stain.

cases, there were antemortem clinical and laboratory evidences of pulmonary hypertension. In the absence of significant pulmonary parenchymal disease or of primary cardiac disease, the pulmonary vascular lesions can be assumed to be responsible for the chronic cor pulmonale.

The cause of the portal venous hypertension in 5 of the cases was cirrhosis of the liver. Several varieties of cirrhosis were found but none was cardiac in type. In 2 of the individuals, organizing portal venous thrombi probably contributed to the portal hypertension. In the sixth case, chronic thrombosis of the portal vein alone was responsible for portal hypertension. These observations suggest two questions: What was the origin of the pulmonary vascular changes? Was there a possible relationship between these pulmonary vascular lesions and abnormalities in the portal venous system?

In 5 cases, emboli or thrombi in varying stages of organization were widespread throughout the small pulmonary arteries. Thrombosis in such vessels is sometimes considered to be a complication of pulmonary hypertension.[15] In the cases under discussion, however, thrombi were too numerous to be explained on this basis. It is most likely that they were the cause of the high pressure rather than its consequence. Although older pulmonary vascular changes in these cases

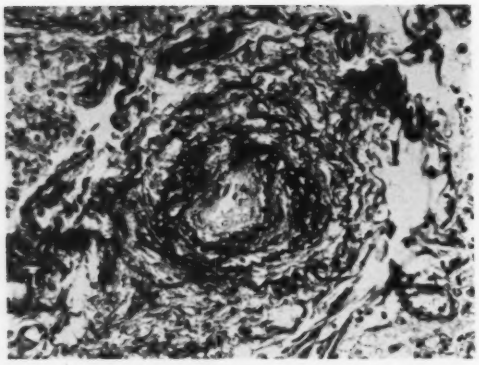

Figure 8

Case 6. Marked proliferation of endothelial cells and fibroblasts in the intima of a pulmonary muscular artery. The internal elastic membrane is reduplicated. Elastic-tissue stain.

were not specifically characteristic, they were suggestive of those lesions that have been shown to follow recurrent pulmonary emboli.[4, 5, 20] These changes varied from moderate arterial intimal proliferation of endothelial cells and fibroblasts to advanced plexiform lesions that resembled recanalized thrombi. These lesions were similar to the changes produced experimentally by the repeated intravenous injection of fragmented blood clots.[16] Two of the patients (cases 1 and 3) had repeated bouts of chest pain, also suggesting recurrent pulmonary emboli.

A possible origin of pulmonary emboli in these cases was the portal venous system and its collateral channels. Hepatic cirrhosis and portal hypertension are common antecedents of portal thrombosis.[21, 22] Portal thrombi were found in 3 of the current cases, 1 of which also had organizing thrombi in collateral varicose esophageal and gastric veins. No other sites of origin for pulmonary emboli were found. In this regard the case of Mantz and Craige[17] is interesting in that recurrent emboli arose from a spontaneously developing portocaval shunt in a patient with portal hypertension. This shunt varied in diameter from 1.5 to 3 cm. An obvious question is whether the collateral channels that bypass the portal system in other cases of portal hypertension are of sufficient size to permit emboli to pass to the lesser circulation. By injection studies Calabresi and Abelmann[29] have demonstrated grossly visible anastomoses of the portal venous bed with the superior vena cava through peri-esophageal, mediastinal, and azygous veins in patients with portal hypertension. All these anastomotic channels were at least 40 μ in diameter and many were apparently far larger. Vessels of this size would probably permit emboli to pass but would obviously limit their size. This would account for the fact that thrombi in the current study were found only in small pulmonary arteries. It would also explain the failure to find pulmonary infarcts, since infarcts usually do not develop when pulmonary emboli are small.[15]

It is also possible that the pulmonary arterial lesions in the current cases arose from intravascular thromboses within the lesser circulation itself. It is well known that the injection of abnormal amounts of thromboplastic substances into the systemic venous circulation is associated with widespread intravenous thromboses.[23] Spaet[24] has reported that the normal portal venous system tolerates much greater quantities of such injected thromboplastic material than does the systemic venous system. If such thromboplastic material were normally present in the portal system, or were present in increased amounts in persons with portal hypertension, one might speculate that its being shunted past the liver would lead to thromboses in the lesser circulation.

Certain other pulmonary vascular abnormalities in these patients were probably a consequence of the pulmonary hypertension rather than part of its cause. These changes included medial muscular hypertrophy in arteries and arterioles as well as occasional instances of arterial necrosis. Medial muscular hypertrophy has been reported in a variety of disorders in which the pulmonary arterial bed has been subjected to high pressure.[13, 25] Necrosis of arterial walls has also been found to be a nonspecific reaction to pulmonary arterial hypertension.[6, 13] In one of our cases (no. 6), necrotizing and inflammatory vascu-

lar changes were extensive and disproportionate to other vascular alterations. This may have been an indication that pulmonary pressure was higher in this case than in other cases or that it was more recent in onset. It is also possible that the necrotizing changes in this individual were not the consequence of hypertension alone. A similar question revolves about the origin of the arteritis so commonly described in other cases of "primary" pulmonary hypertension.[1, 6, 10–12]

Multiple pulmonary arteriovenous fistulas are another possible basis for cor pulmonale in cases of portal hypertension. A case of multiple pulmonary arteriovenous fistulas has been reported in a patient with juvenile cirrhosis.[18] Fistulas were not found in any of the current cases by serial section or injection studies. Recent physiologic investigations of the pulmonary circulation in persons with cirrhosis also have failed to demonstrate such shunts.[26]

Finally, persons with hepatic cirrhosis and portal hypertension may have an increased cardiac output.[19, 27] In the cases previously reported, the increases have not been of sufficient magnitude to cause pulmonary hypertension. However, increased cardiac output might have contributed to the hypertension in the current series. It is well known that persons with a restricted pulmonary vascular bed have a disproportionate rise in pulmonary arterial pressure with rises in cardiac output.[28]

Summary

Six cases are described in which there was a coexisting pulmonary arterial and portal venous hypertension. In 5 of the cases, the pulmonary vascular lesions responsible for the pulmonary hypertension resembled those seen in cases of recurrent embolization. Three of the cases had portal venous thromboses. One of these also had thrombosis of esophageal varices. These thrombi may have been the site of origin for pulmonary emboli. Other possible causes of the pulmonary vascular lesions are also discussed. In one case, there was a severe necrotizing arteritis in the pulmonary arterial tree.

Acknowledgment

I am indebted to Dr. Harry P. Smith, Presbyterian Hospital, New York City, for 3 cases used in this study.

Summario in Interlingua

Es describite sex casos de co-existentia de hypertension pulmono-arterial e porto-venose. In cinque del casos, le lesiones pulmono-vascular responsabile pro le hypertension pulmonar resimilava le lesiones vidite in casos de recurrente embolisation. Tres del patientes habeva thromboses porto-venose. Un de istes habeva etiam thrombosis de varices esophagee. Il es possibile que iste thrombos esseva le sito de origine del embolos pulmonar. Es discutite etiam altere possibile causas del lesiones pulmono-vascular. In un del casos, il habeva sever arteritis necrotisante in le vasculatura arterial del pulmon.

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On Cardiac Murmurs

By AUSTIN FLINT, M.D.

If the murmur in the neck be a propagated murmur it will differ from that at the base of the heart chiefly as regards intensity; the pitch and quality will not be materially changed. If it be rough or soft at the base of the heart, it will be the same in the neck; if the pitch be high or low at the base of the heart, it will be the same in the neck. On the other hand, a murmur produced within the carotid, will be likely, in the great majority of cases to differ in quality and pitch from a coexisting murmur at the aortic orifice.—*Am. J. M. Sc.* n.s. **44**: 29, 1862.

Physiologic Differentiation of Pulmonic Stenosis with and without an Intact Ventricular Septum

By J. I. E. Hoffman, M.D., Abraham M. Rudolph, M.D., Alexander S. Nadas, M.D., and Milton H. Paul, M.D.

WITH THE advent of open-heart surgery it has become more than ever important to differentiate between pulmonic stenosis with an intact ventricular septum (designated as pulmonic stenosis) and pulmonic stenosis with a right-to-left shunt through a ventricular septal defect (tetralogy of Fallot) because of their different operative treatment and operative mortality. Failure to close an associated ventricular septal defect after completely relieving the obstruction to right ventricular outflow may produce a large left-to-right shunt and bring on congestive heart failure;[1-3] if enough obstruction remains, there may be no or little left-to-right shunt but the treatment cannot then be considered ideal.[2]

Unfortunately, attempts to detect the ventricular septal defect at operation by passing a finger down through the pulmonary valve or by looking for an immediate left-to-right shunt into the right ventricle may be unsuccessful. The alternative of performing routine right ventriculotomy would disclose unsuspected ventricular septal defects but has the disadvantage that it could lead to complications like hemorrhage, ventricular rupture,[3] or ventricular aneurysm.[1] An accurate anatomic diagnosis preoperatively is therefore very important and this may usually be done by routine clinical and radiologic examination and electrocardiography.[4-7] There are times, however, when these studies are not adequate to make a definite diagnosis; then aid must be sought from cardiac catheterization with indicator-dilution studies and angiocardiography if necessary. It is the purpose of this paper to present some of the important findings at cardiac catheterization and to relate them to some of the clinical and phonocardiographic signs that help to distinguish pulmonic stenosis from tetralogy of Fallot.

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Dr. Rudolph is an Established Investigator of the American Heart Association.

Material and Methods

Since May 1957 46 patients (25 male and 21 female) with pulmonic stenosis have been catheterized at the Children's Medical Center. Their ages ranged from 6 to 43 years; 8 were under 5, and 13 were 5 to 9 years old. Most of them had moderate or severe pulmonic stenosis, and the clinical features were typical in 37. A pressure gradient from right ventricle to pulmonary artery was demonstrated during cardiac catheterization in 43, and pulmonic stenosis was suggested by clinical findings and angiocardiography in the other 3. Twenty-nine had arterial oxygen saturations over 94 per cent, but 6 of these showed small right-to-left shunts by indicator-dilution curves or a fall of arterial oxygen saturation on exercise; the other 17 had decreased resting arterial oxygen saturations as low as 52 per cent. The atrial level of the shunt was demonstrated by indicator-dilution curves or by finding that peripheral arterial oxygen saturation was similar to that in the left atrium. There were no patients with a left-to-right shunt in this group and none was excluded for this reason.

In the same period 42 patients (20 male and 22 female) with tetralogy of Fallot were catheterized. Their ages ranged from 10 months to 36 years; 15 were under 5, and 13 were 5 to 11 years old. It has not been our practice to catheterize all patients with this diagnosis; these individuals were selected to find out how large the left-to-right shunt was in 4 who were not doing well after anastomotic operations, to study 26 before complete surgical repair, and to investigate 12 who had one or more atypical features (large pulmonary artery, possible left ventricular hypertrophy, split second heart sound, continuous murmur).

Pulmonic stenosis was proved by finding a gradient from right ventricle to pulmonary artery during right heart catheterization in 38 and at

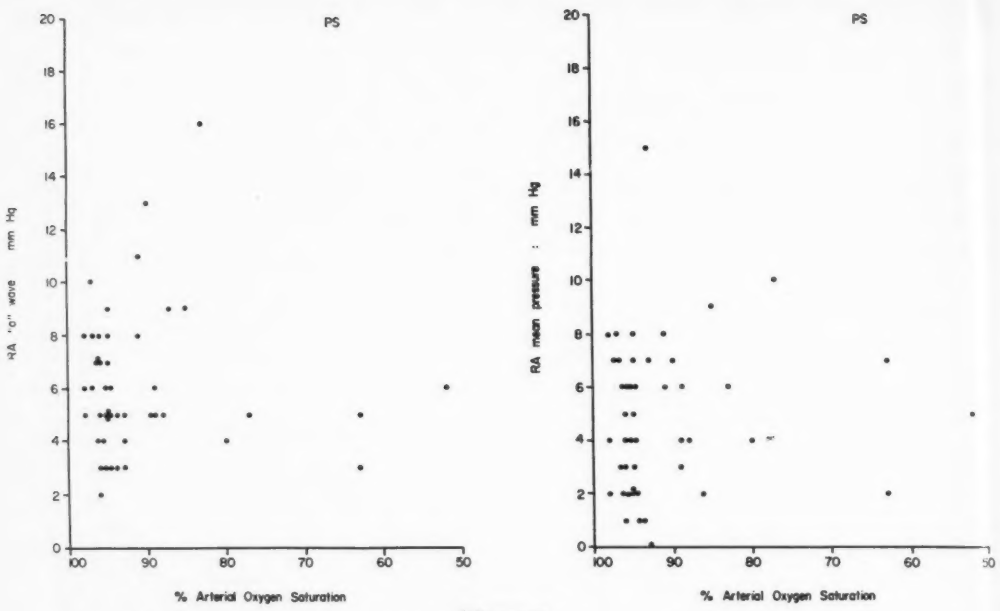

Figure 1

A, left. *Correlation of right atrial (RA) "a" wave and arterial oxygen saturation in pulmonic stenosis.* B, right. *Correlation of right atrial (RA) mean pressure and arterial oxygen saturation in pulmonic stenosis.*

operation in the other 4. The ventricular septal defect was proved by passing the catheter through it in 25 and by operation in 3, and was suggested by indicator-dilution curves in 8 and by angiocardiography in 5; in the remaining one it was inferred from other features. That the great arteries were not transposed was shown by the position of the pulmonary artery at catheterization, angiocardiography, and finding the oxygen saturation of blood in the pulmonary artery to be lower than that in the systemic arteries. In 3 with postoperative left-to-right shunts and 1 with a patent ductus arteriosus the oxygen saturation of pulmonary arterial blood was higher than that in the right ventricle, and 5 others had small left-to-right shunts through the ventricular septal defect.

All patients were studied by routine clinical methods, electrocardiography, x-ray, and fluoroscopy; most had phonocardiograms taken with a Sanborn Twin-Beam photographic recorder. Cardiac catheterization as described recently from this laboratory[8] was carried out in every instance. Right-sided cardiac pressures were recorded through no. 5 to 7 Lehman cardiac catheters ranging from 50 to 100 cm. in length, and arterial pressures were recorded through no. 20 to 22 arterial needles. Simultaneous right ventricular and systemic arterial pressures were measured with separate Statham P23D transducers. The catheter-transducer assemblies had natural frequencies of 25 to 40 cycles per second and, in general, right ventricular pressures tended to be underdamped whereas arterial pressures were sometimes overdamped. Blood oxygen saturation was determined spectrophotometrically;[9] indicator-dilution studies were made by injecting indigo carmine or indocyanine green into the right side of the heart or pulmonary artery and sampling from a systemic artery; and cineangiography as described recently[10] was done in selected cases.

Results

There were "a" waves (measured from the trough of the "y" to the peak of the "a") of 5 mm. Hg or more in 35 of 46 patients with pulmonic stenosis and only 6 of 41 patients with tetralogy of Fallot; none of these 6 was over 7 mm. Hg. The highest "a" waves occurred in patients with pulmonic stenosis who had either no, or only a small, right-to-left shunt and a high right ventricular systolic pressure (figs. 1*A* and 2*A*). Low "a" waves occurred at any arterial oxygen saturation or right ventricular systolic pressure.

Right atrial mean pressures were also low in tetralogy of Fallot and on the average only slightly higher in pulmonic stenosis; the highest mean pressure of 15 mm. Hg was in a boy with severe pulmonic stenosis and pericardial effusion. In pulmonic stenosis the mean pressures in the right atrium correlated only slightly with arterial oxygen saturation and right ventricular systolic pressure (figs. 1*B* and 2*B*).

Pulmonary Artery Pressure

The ranges of pulmonary artery mean pressures were similar in the 2 groups with the exception of 1 boy with tetralogy of Fallot who showed pulmonary arterial hypertension after an aorto-pulmonary anastomosis (fig. 3); the average was slightly higher in pulmonic stenosis. These pressures were not related to right ventricular systolic pressure in either group but the highest pulmonary artery mean pressures tended to occur with the highest arterial oxygen saturations and pulmonary blood flows.

Mean Left Atrial or Pulmonary Artery Wedge Pressures

These measurements were in the normal range for both groups. On the average the mean pulmonary artery wedge pressures alone or pooled with left atrial mean pressures were a little higher in pulmonic stenosis than in tetralogy of Fallot; there were too few left atrial pressure measurements for adequate, separate comparison. No correlation was found with pulmonary blood flow (absolute or relative to body surface area) but there was a tendency for these pressures to be lower at lower arterial oxygen saturations.

The gradients from pulmonary artery to left atrium or pulmonary artery wedge were similar in range and average in the groups except in the boy with pulmonary hypertension.

Pulmonary Blood Flow

Pulmonary blood flow (absolute or relative to the body surface area) varied widely independent of the type of anatomic lesion (figs. 4*A* and 4*B*). The highest flows were in the older and less severely affected patients in each group, and the correlation with arterial oxygen saturation is shown in figure 5.

Right Ventricular-Systemic Artery Systolic Pressure Gradients in Tetralogy of Fallot

In 11 patients pressures in the ascending aorta and right ventricle were recorded in rapid succession when the catheter was passed through a ventricular septal defect, and pressures in 1 were recorded simultaneously from the right ventricle through a venous catheter and from the ascending aorta by a catheter passed retrograde up the aorta (table 1*A*). In all but 2 patients aortic and right ventricular systolic pressures were within 3 mm. Hg of each other, in 1 a rise of 8 mm. Hg on passing from the aorta to the right ventricle was associated with a 7 mm. Hg rise in brachial arterial systolic pressure, and in the patient with a difference of 31 mm. Hg between simultaneous right ventricular and aortic pressure recordings the tracing registered through the aortic catheter was overdamped and that through the venous catheter was underdamped.

Simultaneously recorded right ventricular and peripheral arterial systolic pressures in these same patients differed by as much as +27 to –24 mm. Hg (table 1*B*) and similar systolic pressure gradients were found in another 25 patients in whom comparisons of right ventricular and aortic pressures were not obtained.

Effect of Premature Beats on Ventricular and Systemic Arterial Systolic Pressures

With a premature beat the systolic pressure fell in both ventricles and in the systemic arteries. When the next normal beat occurred the systolic pressure rose near to, or just above, its previous level (usually not more than 10 mm. Hg higher) in the left ventricles and systemic arteries of both groups and with two exceptions in the right ventricle in tetralogy of Fallot (fig. 6). In pulmonic stenosis, however, the postectopic right ventricular systolic pressure was always higher than its previous level by more than 10 mm. Hg; in 27 the maximum increment in right ventricular systolic pressure was 11 to 30 mm. Hg; in 16

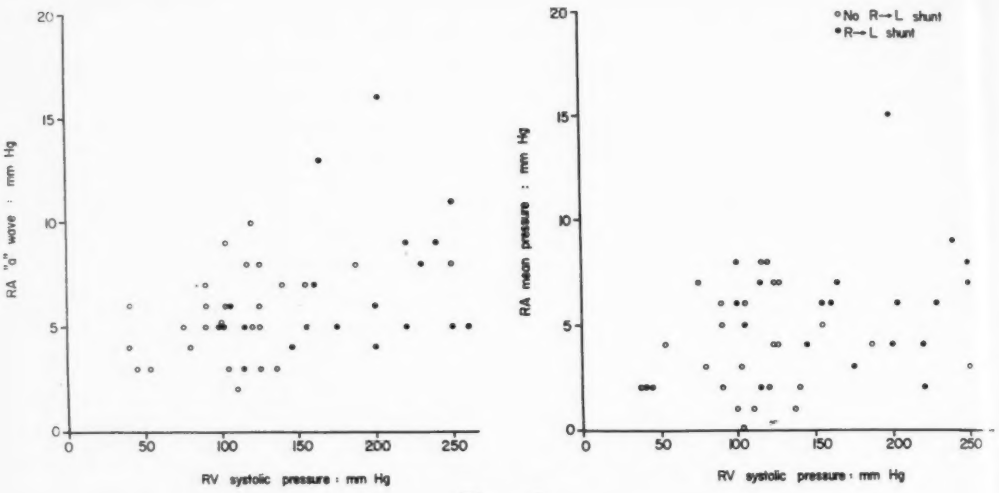

Figure 2

A, left. *Correlation of right atrial (RA) "a" wave and right ventricular (RV) systolic pressure in pulmonic stenosis.* B, right. *Correlation of right atrial mean pressure and right ventricular (RV) systolic pressure in pulmonic stenosis.*

it was 31 to 50 mm. Hg, and in 1 it was 75 mm. Hg. The change in right ventricular systolic pressure was always greater than that in the systemic artery. The maximal postectopic rise in right ventricular systolic pressure in tetralogy of Fallot was 16 mm. Hg, but each time the right ventricular systolic pressure rose above its previous level there was an equivalent rise in the simultaneously recorded systemic arterial systolic pressure (fig. 7).

Shape of the Right Ventricular Pressure Curve

Normally the right ventricular pressure rises rapidly, then rises more slowly (or even falls a little) and then falls rapidly; these 3 phases are usually clearly demarcated from each other.[11, 12] This shape of right ventricular pressure tracing with almost parallel sides and a rounded or flat top was found in all 42 patients with tetralogy of Fallot and also in 15 of 46 patients with pulmonic stenosis. The remaining 31 patients with pulmonic stenosis had triangular right ventricular pressure curves in which these distinct phases were not shown (fig. 8).

In an attempt to assess curve shape objectively a ratio was made of the width of the right ventricular pressure curve 30 per cent below its systolic peak to its width 30 per cent above zero baseline (or 20 per cent above and below systolic pressure divided by 2). This ratio was more consistent than ratios of widths nearer the top and bottom of the curve, but still varied at different times during catheterization. In 40 patients the maximum differences in ratios (each the average of 3 successive curves) varied from 0 to 23 per cent; 23 differences were 5 per cent or less, and all but 3 were under 13 per cent. These variations could not always be attributed to differences in damping, which at times did not alter the ratio. Errors of measurement were estimated to account for a maximum variation of ±5 per cent at a paper speed of 100 mm. per second at which most of these ratios were measured.

In figure 9 are the ratios for the right ventricle in pulmonic stenosis and tetralogy of Fallot, with the left ventricular ratios from both groups for comparison. Generally, the right ventricular ratios in tetralogy of Fallot were similar to those for the left ventricle and higher than those for pulmonic stenosis but discrimination between the 2 groups was poor because many with pulmonic stenosi-

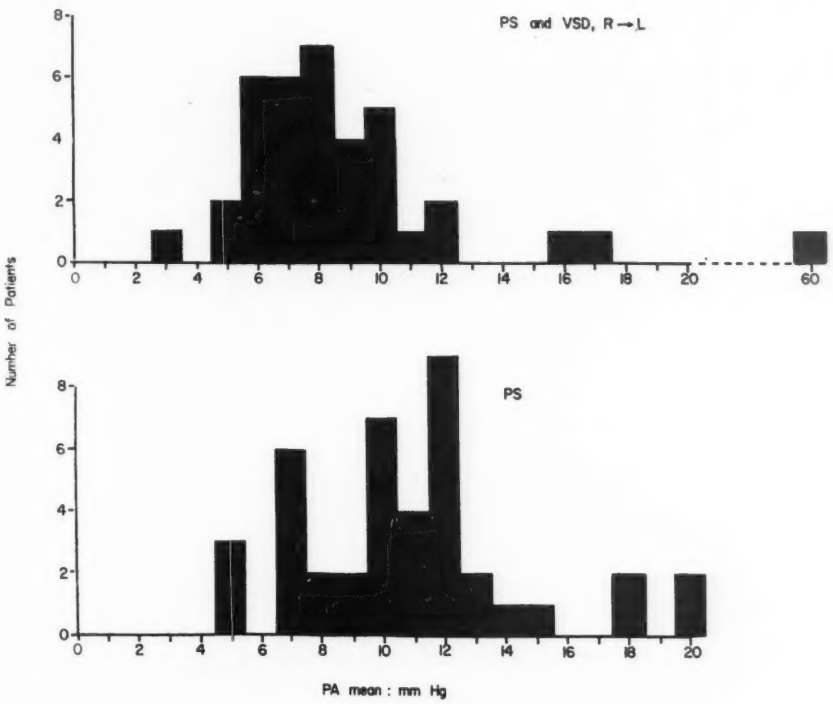

Figure 3

Frequency distribution of pulmonary arterial (PA) mean pressure in tetralogy of Fallot (PS, VSD, R→L) and pulmonic stenosis (PS).

had high ratios. In pulmonic stenosis there was no consistent relationship between the ratio and the right ventricular systolic pressure or the arterial oxygen saturation (fig. 10).

Site of the Stenosis

The site of the stenosis may be assessed at cardiac catheterization by noting on the fluoroscopic screen the position of the catheter tip as the pulmonary arterial pressure tracing changes to a right ventricular pressure tracing, by inspecting the pressure tracings for evidence of an infundibular chamber, and by angiocardiography. Confirmation of this assessment may be obtained when the heart is examined at operation or autopsy.

In pulmonic stenosis the site of pressure change was judged to be at the level of the valve in 35 of 43 patients; 17 of these were confirmed at open-heart operation and 1 was found to be subvalvular. Five others were thought to have valvular and infundibular stenosis, and at open-heart operation in 3 there was 1 with double stenosis but the other 2 had only valvular stenoses. Three were thought to have pure infundibular stenosis,[33, 34] and this was proved in the only one operated on. In the patients with pulmonic stenosis a Bernouilli effect (a negative systolic pressure in the pulmonary arterial tracing) was present in 22, absent in 17, and doubtful in 2. It was not related to arterial oxygen saturation but was absent in all 4 patients whose right ventricular systolic pressures were below 60 mm. Hg and absent in only 2 of 9 with right ventricular systolic pressures over 160 mm. Hg. In 1 patient it occurred on passage of the catheter from the infundibulum into the body of the right ventricle.

In tetralogy of Fallot the stenosis was thought to be valvular in 7, valvular and infundibular in 14, infundibular in 10, and of

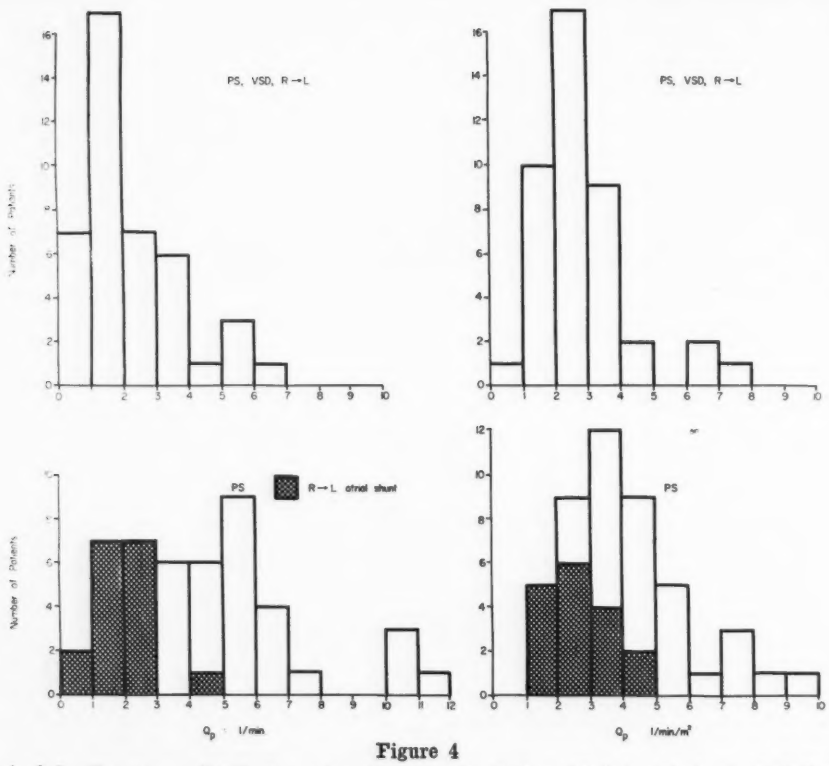

Figure 4

A, left. *Frequency distribution of pulmonary blood flow (Q_p) in tetralogy of Fallot (PS, VSD, R→L) and pulmonic stenosis (PS).* B, right. *Frequency distribution of pulmonary blood flow index (Q_p) in tetralogy of Fallot and pulmonic stenosis.*

undetermined site in 7. There was only moderate correlation between these estimates and the findings at angiocardiography or open-heart operation. A Bernouilli effect was definite in 7 and probable in another 2; all but 1 had valvular stenoses and 2 had additional infundibular stenoses. The arterial oxygen saturation of these 9 patients ranged from 72 to 95 per cent, and pulmonary blood flow was markedly reduced in 4 of them.

Obstruction of the Right Ventricular Outflow Tract by the Catheter

This obstruction occurred in 3 of 43 patients with pulmonic stenosis and 4 of 38 with tetralogy of Fallot. All 3 with pulmonic stenosis had marked valvular stenosis and right-to-left shunts, though in 1 the arterial oxygen saturation was 96 per cent; 3 of those with tetralogy of Fallot had infundibular stenosis. During obstruction by the catheter 2 patients in each group showed abnormal signs or symptoms (restlessness, vomiting, bradycardia, cyanosis, pallor) and the arterial oxygen saturations measured at this time in 3 patients were 11, 14, and 15 per cent.

Time of Closure of the Aortic and Pulmonic Valves

The relative times of closure of the semilunar valves may be determined by identifying the two components of the second heart sound on the phonocardiogram. In tetralogy of Fallot the second heart sound is usually single but is sometimes narrowly split (fig. 11). By contrast, in pulmonic stenosis the second heart sound is usually widely split (fig. 12), and this may be noted even when the pulmonary blood flow and pressure are as low as those found in tetralogy of Fallot.

It is also possible to infer the times of

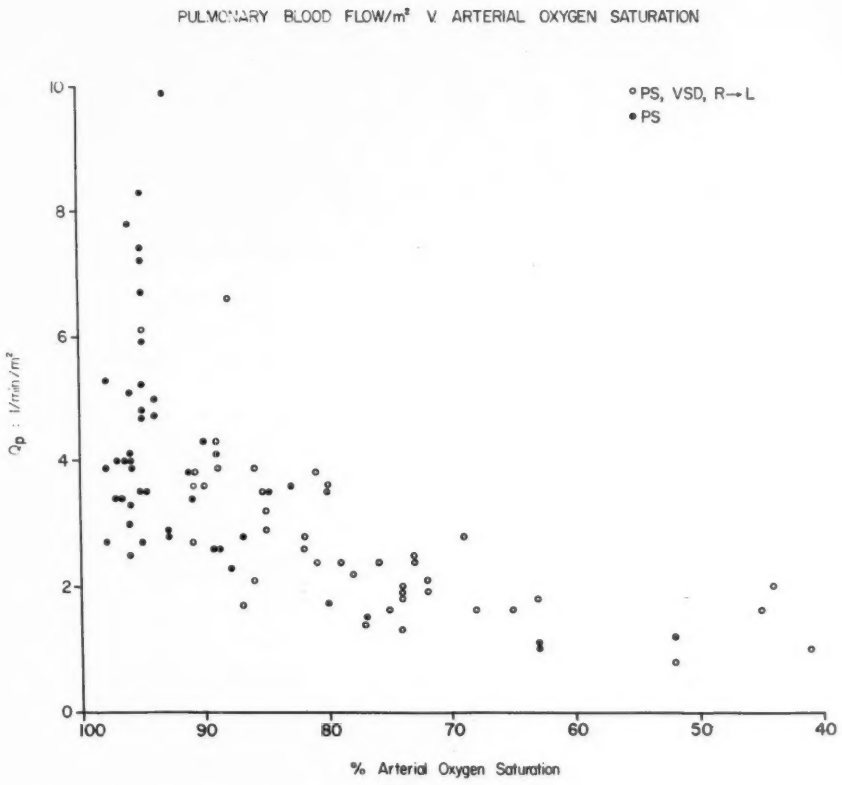

Figure 5

Correlation of pulmonary blood flow index (Q_p) and arterial oxygen saturation in tetralogy of Fallot and pulmonic stenosis.

semilunar valve closure from the pressure tracings. Aortic valve closure occurs at the time of the dicrotic notch of the central aortic pulse or approximately at that point on the descending limb of a left ventricular pressure curve that corresponds to the dicrotic notch pressure of a peripheral arterial pulse. Pulmonic valve closure may be similarly determined from pulmonary arterial and right ventricular pressure tracings, and if the dicrotic notch is not well defined, the use of pulmonary arterial mean pressure introduces little error. In 7 patients with severe pulmonic stenosis the delay of pulmonic valve closure with respect to aortic valve closure was 0.06 to 0.14 second (mean 0.09 second), whereas in 1 patient with mild pulmonic stenosis the difference was only 0.02 second. In tetralogy of Fallot the maximum measured delay was 0.07 second, and the average difference for 21 patients (many of them with marked stenosis) was 0.005 second.

To obviate errors due to measurement or to alteration of the heart rate simultaneous pressure tracings were obtained from right and left ventricles in patients with pulmonic stenosis and tetralogy of Fallot (fig. 13); the similarity of the 2 tracings in tetralogy of Fallot and the prolongation of the right ventricular pressure curve in pulmonic stenosis are well known.

Discussion

Right Atrial Pressures

The normal atrial "a" waves and mean pressures in tetralogy of Fallot and their elevation in some patients with pulmonic stenosis confirm previous reports.[4, 5, 7, 14–16] In pulmonic stenosis the inverse relationship be-

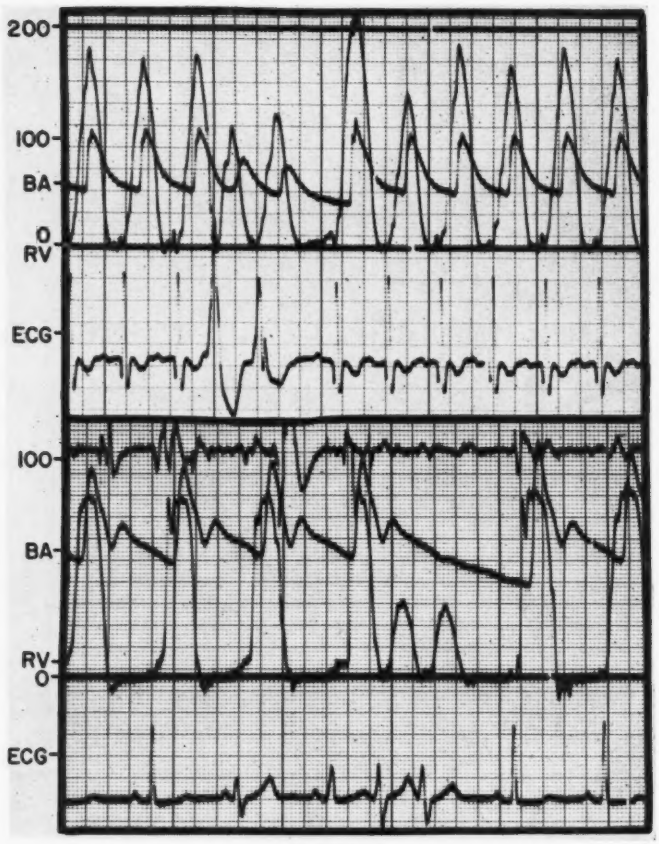

Figure 6

Top. *In pulmonic stenosis after ectopic beats the right ventricular (RV) systolic pressure rose 36 mm. Hg above its previous level while simultaneous brachial arterial (BA) systolic pressure rose only 12 mm. Hg.* Bottom. *In tetralogy of Fallot after ectopic beats the right ventricular (RV) systolic pressure and the simultaneous brachial arterial (BA) systolic pressure rose 5 mm. Hg.*

tween right atrial pressures and peripheral arterial oxygen saturation (figs. 1 and 2) may depend on the size of the interatrial communication. Some patients with large right-to-left shunts and marked clinical disability (severe limitation of effort, large hearts) had low right atrial and merely moderately raised right ventricular systolic pressures (about 100 mm. Hg) and this might be explained by the presence of a large patent foramen ovale or atrial septal defect.[17] A large interatrial communication could decompress the right atrium, and right ventricular contraction could be impaired by loss of distending pressure or volume from the right atrium[14] or by inadequate myocardial oxygenation. This large interatrial communication could also explain cyanosis dating from birth. By contrast, other patients have smaller interatrial communications and can achieve similar sized or smaller right-to-left shunts only by elevating their right atrial pressures.

Pulmonary Arterial and Left Atrial Pressures

Slight differences between the average pulmonary artery mean pressures in these

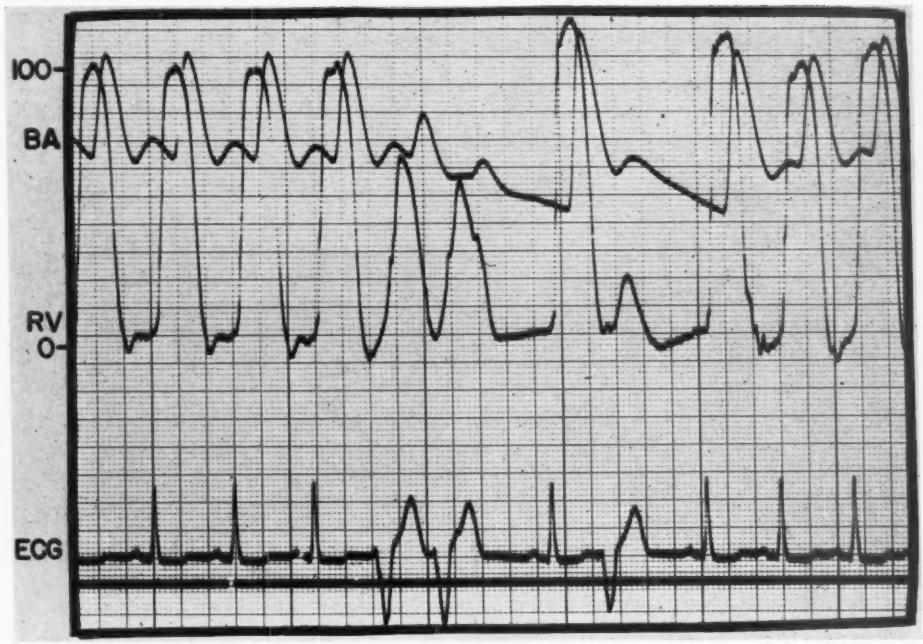

Figure 7

Simultaneous rise in right ventricular and brachial arterial systolic pressures after ectopic beats in tetralogy of Fallot.

groups and between the left atrial (or pulmonary arterial wedge) pressures have been reported before[7, 15] and could have been due to the correlations between these mean pressures and pulmonary blood flow. In the present study more of the pulmonic stenosis group had normal pulmonary blood flows and arterial oxygen saturations and when allowance was made for this variation there seemed to be little difference between the 2 groups. Possibly these factors influence pulmonary arterial and left atrial pressures to similar extents, and this may explain why the pressure gradients across the pulmonary vascular bed were similar in the 2 groups. For blood to continue to flow through the lungs there must be at least a minimal gradient between the pulmonary artery and the left atrium; since the left atrial pressures are normal in both groups, this gradient sets a lower limit for pulmonary arterial pressure that cannot be reduced.

Ventricular and Systemic Arterial Pressures

The similarity between systolic pressures in right and left ventricles, aorta, and peripheral arteries has been noted previously,[5, 7, 15, 18, 19] but in most reports right ventricular and systemic pressures were not measured simultaneously and differences between central and peripheral pulses were not stressed. Table 1 of the present study shows that when pulmonic stenosis was associated with a right-to-left shunt through a ventricular septal defect, the systolic pressures measured in the right ventricle and aorta were almost identical. That in the same patient there could be greater systolic pressure gradients between right ventricle of aorta and a peripheral artery (table 1) may be explained by several factors:

1. Systolic pressure in the peripheral artery is usually higher than that in the ascending aorta because of reflected waves or arterial resonance.[20-24] This observation can be easily

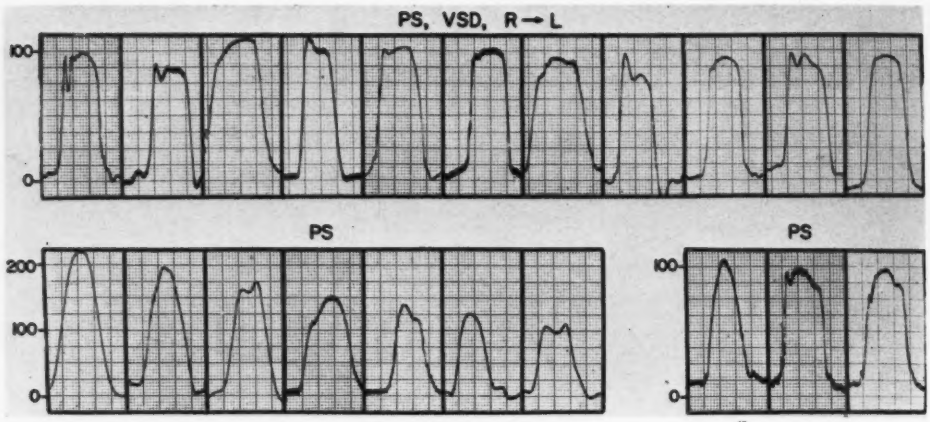

Figure 8

Top. Right ventricular pressure curves in tetralogy of Fallot; in general they have flat or rounded tops, well demarcated from the rapidly rising and falling sides. Bottom. *Right ventricular pressure curves in pulmonic stenosis (2 amplifications). Many but not all curves are triangular with no well-defined ejection plateau. The last 2 curves at the higher amplification occurred at different times during catheterization of 1 patient and demonstrate the variability of curve shape.*

confirmed by withdrawing a retrograde catheter from the ascending aorta toward the peripheral artery through which it was inserted. In one patient with tetralogy of Fallot, for example, the femoral arterial systolic pressure was 12 mm. Hg higher than that in the ascending aorta when measured through the same catheter, and 14 mm. Hg above it when measured simultaneously through an arterial needle. In another patient the femoral arterial systolic pressure was 23 mm. Hg above that in the ascending aorta when measured through the same catheter.

2. Simultaneous systolic pressure gradients of this magnitude between aorta and peripheral artery (measured through a catheter and an arterial needle respectively and with use of separate transducers) were found in 6 patients in this series but in 10 others the systolic gradient was less negative or even positive. Diastolic pressures differed little, if at all. In most patients these variations in systolic pressure gradients could be related to overdamping of the peripheral arterial pressure tracings relative to those in the right ventricle or aorta; this would decrease or even reverse the normal negative central-peripheral systolic pressure gradient. The magnitude of the effect due to damping is well shown by two examples. In one patient 2 venous catheters were passed into the right ventricle and the simultaneous pressures were 111 to 9 and 125 to 6. In another patient the first right ventricular pressure was taken when the venous catheter had been filled with blood to damp the tracing, the second as soon as it had been flushed with saline. With little change in the accompanying arterial pressure there was a change of 22 mm. Hg in the right ventricular systolic pressure.

An additional source of variation is added when the pressures are measured simultaneously with different transducers, for these and their amplifying systems may not be exactly matched; with care this variation is usually small.

3. When arterial pressure is measured by an arterial needle that faces the direction of blood flow, the recorded pressure will exceed the hydrostatic or lateral pressure by an amount equivalent to the kinetic energy of flow at that point. For a velocity of flow of 100 cm. per second this excess would be about 4 mm. Hg and for a velocity of 200 cm. per

second it would be about 15 mm. Hg. Conversely, when a catheter faces away from the direction of flow, it registers a pressure lower than the hydrostatic pressure because of suction at its tip; this decrement cannot be calculated exactly, but is less than 4 mm. Hg at a velocity of 100 cm. per second.[25–27] Velocities in large arteries have been estimated at 100 to 125 cm. per second, with normal outputs,[28–30] so that differences due to increments and decrements of kinetic energy are unlikely to exceed 10 mm. Hg.

These factors could explain the discrepancies between tables 1*A* and 1*B*, so that the finding of a systolic pressure gradient up to ±30 mm. Hg between right ventricle and a peripheral systemic artery is still compatible with a negligible gradient between that right ventricle and the aorta. The same factors could, of course, accentuate or mask a real but moderate gradient between these sites, although in none of these patients could this gradient have been big. In fact, the data suggest that a large ventricular septal defect allows rapid equilibrium of pressure on its two sides, so that the right ventricular systolic pressure would not differ much from that in the left ventricle and aorta. This is not incompatible with a large flow from right ventricle to aorta, for in health there is usually little gradient from a ventricle to the artery it discharges into; furthermore, measurements of maximum systolic pressures may obscure larger and more significant phasic gradients existing at certain instants of the cardiac cycle.

Response to Premature Beats

The marked difference between the 2 groups in the rise of right ventricular systolic pressure after premature beats confirms the hypothesis of rapid pressure equilibration in tetralogy of Fallot. This method of distinguishing the 2 groups has proved of great value when the right ventricular systolic pressure has been at the systemic level and it has not been known whether or not there was an associated ventricular septal defect. In practice, it is necessary to record enough

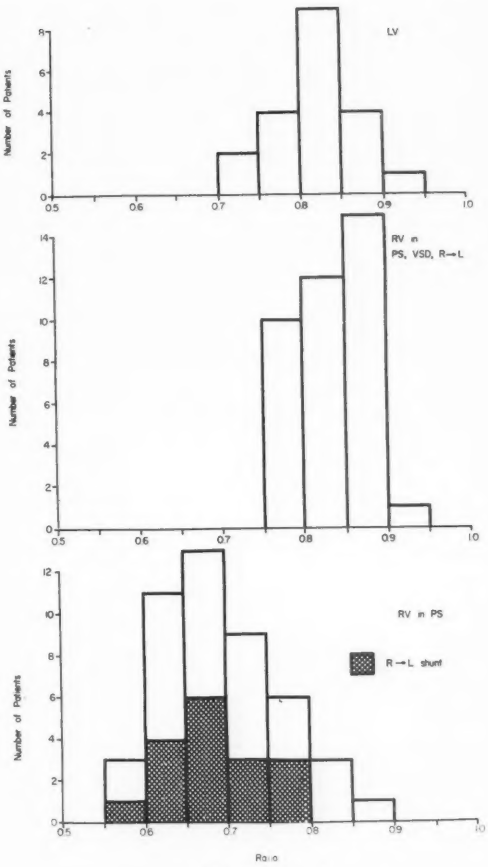

Figure 9

Frequency distribution of the ratio width of ventricular pressure curve 30 per cent below systolic peak to width of curve 30 per cent above zero. LV, left ventricle; RV, right ventricle.

ectopic beats to be sure that the maximal postectopic rise has been observed and to secure simultaneous systemic arterial and right ventricular pressures.

Shape of the Right Ventricular Pressure Curves

Another consequence of the rapid equilibration of pressure across the ventricular septal defect is that the pressure curves in the right and left ventricles would be similar in shape (figs. 9 and 10). This type of ventricular pressure tracing with almost parallel sides and a flat or rounded top (ejection plateau) represents ventricular contraction against a

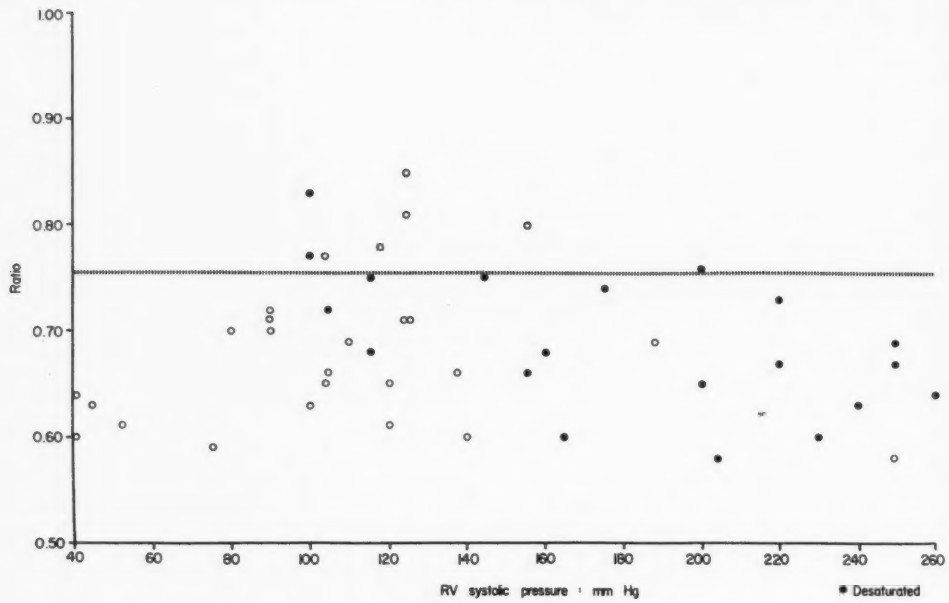

Figure 10

Correlation of curve ratio and right ventricular systolic pressure in pulmonic stenosis. The dotted line represents the lower limit of the RV (right ventricle) ratio in tetralogy of Fallot.

normally changing outflow resistance[11, 12] and was found in all patients with tetralogy of Fallot. By contrast, when there was pulmonic obstruction with an intact ventricular septum, the pressure tracings were often triangular with pointed tops;[5, 7, 11, 31] this is similar to what Fineberg and Wiggers[12] found in experimental pulmonary artery obstruction and ascribed to a more isometric type of ventricular contraction. In distinction to the findings of Bouchard and Cornu,[31] however, there were many with pulmonic stenosis whose right ventricular pressure curves resembled those in tetralogy of Fallot (figs. 8 to 10). This might indicate differences in ventricular responses to pulmonary valvular obstruction, variable infundibular hypertrophy, or perhaps artifacts due to the position of the catheter; at different times during cardiac catheterization the curve shape may vary not only in the curve ratio but also in the shape of the peak. Whatever the reasons for this variation in curve shape in pulmonic stenosis it makes this an unreliable criterion for distinguishing the 2 groups in the range in which their right ventricular systolic pressures are near systemic levels.

Site of the Stenosis

Since the exact position of the pulmonic valve cannot be seen at fluoroscopy, it is difficult to be sure of its relation to the catheter tip when the change from pulmonary arterial to right ventricular pressure takes place; it is particularly difficult to detect a subvalvular stenosis that may be only a few millimeters below the valve. If the infundibular stenosis is further from the valve, it may be detected more easily but can be missed if the infundibular chamber is short, if the catheter tip slips back rapidly into the body of the right ventricle, if pulmonary arterial and infundibular pressures are very low or damped, or if multiple ectopic beats prevent the recording of a stable pressure from the outflow tract of the right ventricle. On the other hand, an infundibular chamber may be falsely diag-

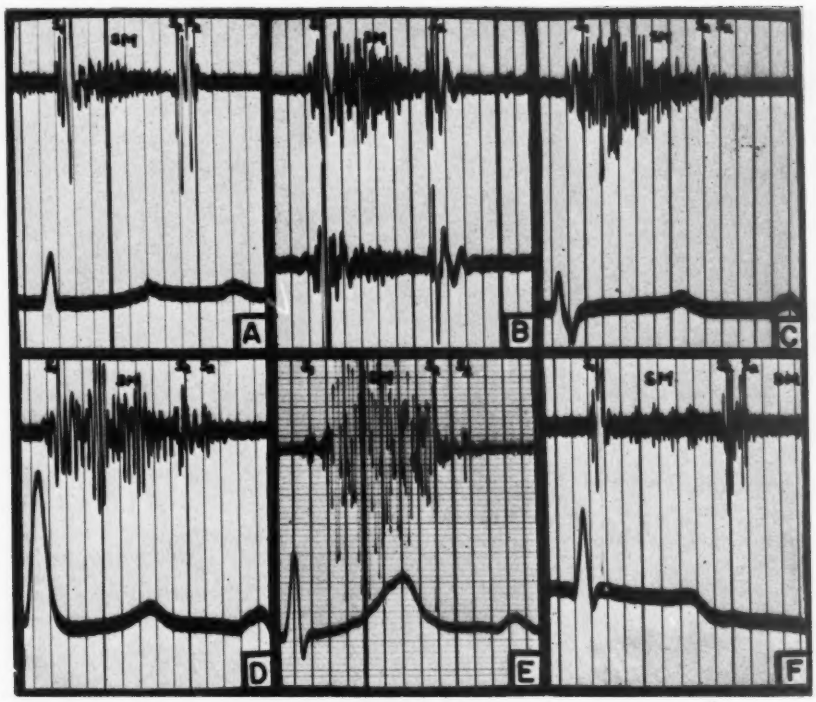

Figure 11

Phonocardiograms in tetralogy of Fallot. Speed 75 min. per sec. Time interval 0.04 sec.

Patient	Pressures mm. Hg RV Systolic	PA Mean	Pulmonary Flow (L./Min./M.²)	Arterial O₂ %	Splitting of S_2 (sec.)
A	...	..		Very severe disease	*0.03*
B	*100*	*6*	*0.8*	*52*	*0.02-0.04*
C	*88*	*8*	*3.8*	*91*	*0.04-0.05*
D	*110*	*10*	*3.6*	*91*	*0.05*
E	*115*	*8*	*6.1*	*95*	*0.07*
F	*115*	*16*	*4.3*	*89*	*0.04*

S_1, first heart sound; S_2, second heart sound; SM, systolic murmur; DM, diastolic murmur; RV, right ventricle; PA, pulmonary artery.

nosed if intermittent occlusion of the catheter tip by the wall of the right ventricular outflow tract produces a low systolic pressure there. Angiocardiograms may also be misinterpreted; in particular, if the pulmonary blood flow is very small, it is possible to miss a valvular stenosis that is associated with an infundibular stenosis.

Whether an anatomic infundibular stenosis exists with or without a pressure gradient depends partly on definition. In 2 patients with large systolic pressure gradients between the right ventricular infundibulum and body, the right ventricular outflow tract was seen on cineangiography to constrict in systole and to dilute widely in diastole. Evidently the infundibular gradient and stenosis here due to marked hypertrophy of the muscle of the crista supraventricularis, and similar hypertrophy was found in many patients at open-heart operation even if no gradient had been found at cardiac catheterization. After valvotomy this gradient may become manifest[32, 33] but as long as the obstruction is due to muscle and not to fibrous tissue it has been our experience (based on recatheterization in

Table 1

Comparison of Pressures in Right Ventricle, Aorta, and Peripheral Artery in Tetralogy of Fallot

A. Right ventricle and aorta			B. Right ventricle and peripheral artery		
Right ventricle	Aorta	Systolic gradient RV-aorta	Right ventricle	Peripheral artery	Systolic gradient RV-peripheral artery
109/8	112/52	−3	123/11	96/64 BA	+27*
			108/−1	97/54	+11*
83/−7	83/45	0	93/1	89/48 FA	+4*
115/−	113/73	+2	115/−	134/80 BA	−19
(134/80	132/75)		114/4	138/82	−24
119/1	119/66	0	111/4	119/69 FA	−8
(128/71	129/67)		119/1	128/71	−9*
105/5	104/64	+1	82/10	88/45 FA	−6
92/0	95/63	−3	92/1	92/57 BA	0*
(97/58	99/60)		92/0	97/58	−5*
97/0	89/59	+8	97/0	79/68 BA	+18*
(79/68	72/60)				
108/7	108/67	0	125/10	99/65 BA	+26*
(100/70	100/70)		108/7	100/70	+8*
82/5	80/52	+2	82/5	83/52 FA	−1
(82/52	82/51)				
96/0	96/54	0	104/4	106/56 FA	−2*
91/0	90/64	+1	128/2	143/88 FA	−15
137/6	106/82	+31*	137/6	118/84 FA	+19*

*Second tracing overdamped relative to first tracing.
Figures in parentheses are simultaneous peripheral arterial pressures.
BA, brachial artery; FA, femoral artery.

a few and on clinical and electrocardiographic evidence of regression of right ventricular hypertrophy) that it will regress with time.

Infundibular stenosis was diagnosed at cardiac catheterization more often in patients with tetralogy of Fallot as found by many other workers.[4–7, 33] Agreement among estimates of the site of the stenosis obtained from pressure tracings, cineangiocardiography and open-heart operation was only moderately good. These estimates may never agree completely, partly because of the technical difficulties mentioned earlier and partly because to some extent these three ways of estimating stenosis measure different aspects of it.

As expected, the Bernouilli effect was found usually when there was valvular stenosis, for its production depends on the passage of a narrow jet of fluid into a relatively dilated tube; there can, however, be an associated infundibular stenosis and rarely this may be the only site of stenosis. The Bernouilli effect was not always found when there was valvular stenosis. We were unable to confirm or deny the contention of Bouchard and Cornu[31] that these exceptions depend on the shape of the valve but agree with them that the effect may be missed if the catheter is withdrawn from the pulmonary artery too rapidly. The absence of this phenomenon in mild pulmonic stenosis may also be explained by an insufficient change in the dynamics of blood flow through the valve.

Catheter Obstruction of the Outflow Tract

The signs, symptoms, and hemodynamic features that follow obstruction of a stenotic pulmonary valve by a catheter have been de-

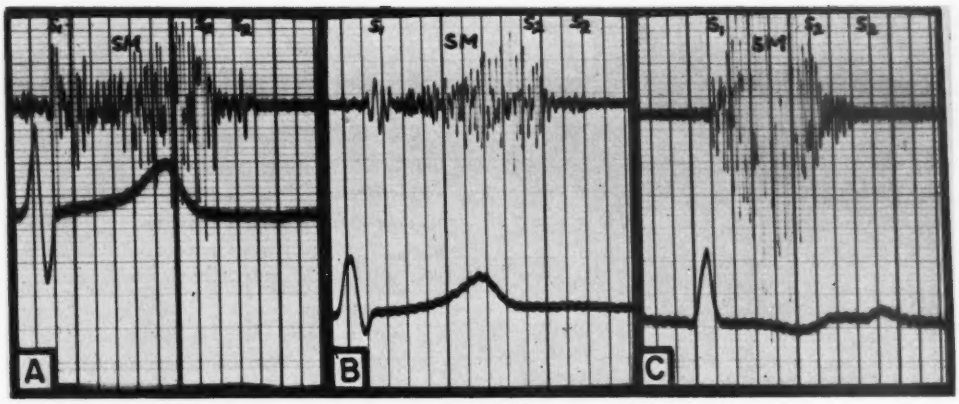

Figure 12

Phonocardiograms in pulmonic stenosis. Speed 75 mm. per sec. Time markings 0.04 sec.

Patient	Pressures mm. Hg RV Systolic	PA Mean	Pulmonary Flow (L./Min./M.²)	Arterial O_2 %	Splitting of S_2 (sec.)
A	*125*	*12*	*5.3*	*98*	*0.08*
B	*125*	*12*	*3.4*	*97*	*0.08-0.09*
C	*220*	*10*	*2.3*	*88*	*0.11*

S_1, first heart sound; S_2, second heart sound; SM, systolic murmur; RV, right ventricle; PA, pulmonary artery.

scribed.[13] All but one of the patients in that report had valvular pulmonic stenosis with an intact ventricular septum, but the phenomenon has also been encountered when the stenosis has been infundibular and associated with a ventricular septal defect. It is thus not the anatomic type of lesion but rather the narrowness of the outflow tract relative to the diameter of the catheter that permits obstruction to occur. Both in pulmonic stenosis and tetralogy of Fallot the arterial oxygen saturation may drop to dangerously low levels.

Phonocardiographic Signs

The final consequence of the presence or absence of a ventricular septal defect when there is pulmonic stenosis is shown in the auscultatory signs of these two lesions. When the ventricular septum is intact, right ventricular systole is prolonged abnormally beyond left ventricular systole: this leads to two of the cardinal phonocardiographic and auscultatory signs, namely, the widely split second heart sound and the extension of the systolic murmur beyond the aortic component of the second heart sound.[35-37] By contrast, when pulmonic stenosis is associated with a right-to-left shunt through a ventricular septal defect, the second sound is usually single or narrowly split and the systolic murmur does not pass beyond it.[37] Leatham[35] has argued that right ventricular ejection is prolonged in these cases as well but that pulmonic valve closure is not heard long after aortic valve closure because of the very low pulmonary blood flow and pulmonary arterial pressure. The following points, however, may be cited as strong evidence that right ventricular systole is not prolonged in tetralogy of Fallot and that aortic and pulmonic valve closure are close together or even simultaneous:

1. Pulmonary blood flow and pulmonary arterial pressure may be equally low in the 2 groups (figs. 3, 5, and 6). Even when low in pulmonic stenosis they may be associated with detectable wide splitting of the second heart sound and passage of the systolic murmur beyond aortic valve closure (fig. 12).

2. In some patients with tetralogy of Fallot the second heart sound may be narrowly split (fig. 11). The widest split in our series was

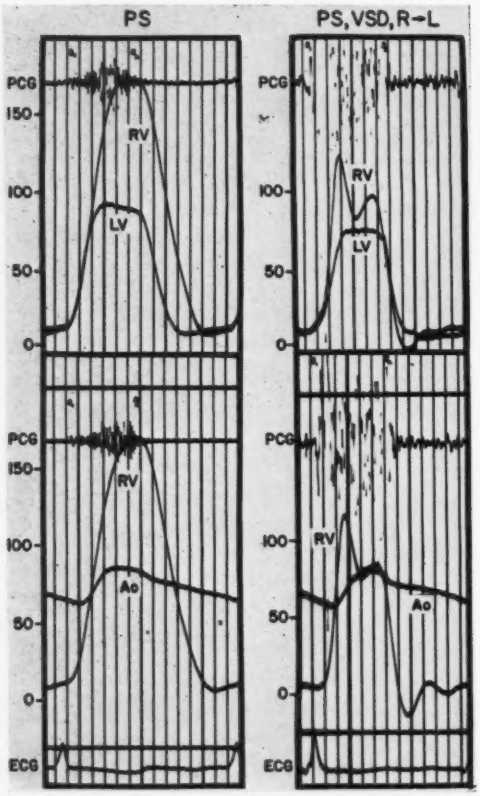

Figure 13

Simultaneous right (RV) and left (LV) ventricular pressure curves (top) *and right ventricular (RV) and aortic (Ao) pressure curves* (bottom), *in pulmonic stenosis and tetralogy of Fallot. The phonocardiograms (PCG) were taken by external microphone at the same time. S_1, first heart sound; S_2, second heart sound.*

0.07 second in a boy who had very little right-to-left shunt and was therefore to some extent like a patient with pulmonic stenosis.

3. After a successful anastomosis between the pulmonary artery and the aorta or subclavian artery the pulmonary arterial blood flow and pressure rise. Nevertheless, the second heart sound has in our experience always remained single or narrowly split as would be expected because the equilibration of right and left ventricular pressures is not affected by the anastomosis. In 4 patients with tetralogy of Fallot studied by cardiac catheterization after anastomotic operations the right ventricular pressure curves showed all the characteristics of tetralogy of Fallot described in this paper. The phonocardiogram of one of them (fig. 11*F*) demonstrated the closely split second heart sound.

4. In tetralogy of Fallot the right and left ventricular pressure tracings are similar in shape with rapid pressure falls at the end of systole. This is particularly well shown in simultaneous pressure tracings (fig. 13).

5. Measurements of the pressure tracings have failed to reveal marked delay of pulmonic closure in tetralogy of Fallot although this marked delay was found in pulmonic stenosis and the differences were great despite allowance for errors of measurement. Alignment of pulmonic valve closure (and the pulmonic component of the second heart sound) with the time when the right ventricular pressure falls below that in the pulmonary artery may be incorrect if the pressure in an infundibular chamber is sustained beyond that in the body of the right ventricle, and if the stiffness of the pulmonary valves leads to delay in their closure. Our own observations (fig. 14) and those of Rodbard and Shaffer[38] show that pressure in the infundibular chamber falls with or before the pressure in the body of the right ventricle, though there may be patients in whom this does not happen. Increased stiffness of the pulmonary valves has not to our knowledge been investigated so far but it is unlikely to be of paramount importance because in pulmonic stenosis in which the pulmonary valve is known to be thick and often stiff, the delay of the pulmonic component of the second heart sound matches the delay in the reversal of the right ventricular-pulmonary artery pressure gradient. There is no good reason why this should differ in patients with tetralogy of Fallot, in many of whom, moreover, the stenosis is infundibular and not valvular.

Another phonocardiographic distinction between the 2 groups was made by Vogelpoel and Schrire[37] and has been confirmed and emphasized here. In tetralogy of Fallot the systolic murmur begins early and dominates

the first half of systole, whereas in pulmonic stenosis it begins later and dominates the second half of systole. The difference is probably related to the more rapid right ventricular pressure rise and thus more rapid right ventricular ejection in tetralogy of Fallot, and may serve as a more sensitive index of the rate of right ventricular ejection than does the shape of the right ventricular pressure curve. Uncommonly the systolic murmur has been midsystolic in a few in each group and three times has been late in tetralogy of Fallot; in each of these exceptions, however, the distinction between the 2 groups could be made by the splitting of the second heart sound and the relation of the end of the systolic murmur to it. At present it is not possible to explain how these variations come about. Nevertheless, it is usually possible with all the phonocardiographic features to make a diagnosis of pulmonic stenosis or tetralogy of Fallot and to infer from them some of the important hemodynamic changes in each lesion.

These distinctions may not hold when there is pulmonic stenosis and ventricular inversion (corrected transposition). We have seen 3 patients with this syndrome whose phonocardiograms were typical of tetralogy of Fallot although there was no evidence of a ventricular septal defect at cardiac catheterization. Although ventricular inversion is commonly associated with a ventricular septal defect, this is not invariable, so that in the absence of anatomic proof of the intactness of the ventricular septum in these 3 patients we should reserve judgment about the value of phonocardiography in distinguishing pulmonic stenosis from tetralogy of Fallot in this syndrome.

Differential Diagnosis between Pulmonic Stenosis and Tetralogy of Fallot

A definitive distinction between pulmonic stenosis and tetralogy of Fallot short of right ventriculotomy is admittedly difficult. The only preoperative proof of the existence of an associated ventricular septal defect is the passage through it of the cardiac catheter

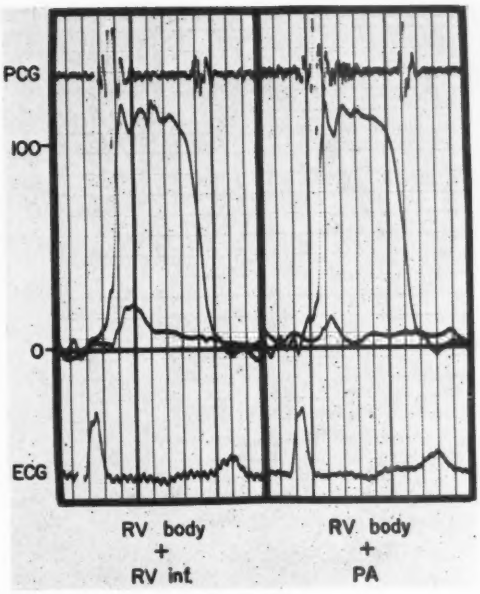

Figure 14

Pressure curves taken simultaneously in right ventricular body and infundibulum (left) *and in right ventricular body and pulmonary artery* (right) *in tetralogy of Fallot. All curves recorded at same sensitivity. PCG, phonocardiogram; ECG, electrocardiogram.*

from the right ventricle to the left ventricle or aorta. Failing this, the presence of an associated ventricular septal defect may be strongly suspected in the following circumstances:

1. The right ventricular pressure curve has a flat or rounded top and almost parallel sides, the right ventricular systolic pressure is within the systemic range, and after ectopic beats the right ventricular systolic pressure does not rise more than 10 mm. Hg and does not separate from the systemic systolic pressure.

2. A right-to-left shunt is shown by injection of an indicator dye into the right ventricle. This does not provide unequivocal proof that the shunt takes place through a ventricular septal defect for, if there is tricuspid regurgitation and a right-to-left atrial shunt, indicator-dilution curves may not demonstrate the level of the shunt. A good selective cineangiogram after injection of radio-

paque dye into the right ventricle should reduce or abolish this source of error and has the additional advantage of showing the anatomy of the right ventricular outflow tract and pulmonary arteries. It is also possible to miss the right-to-left shunt through the ventricular septal defect if the indicator or dye is injected into the outflow region of the right ventricle beyond the defect or, when the right-to-left shunt is very small, if the indicator or dye is injected into the body of the right ventricle but not into the small stream that passes through the defect.

3. The site of the stenosis is shown to be infundibular. The limitations of cardiac catheterization in defining the site of the stenosis have already been discussed and it is also true that infundibular stenosis does occasionally occur in pulmonic stenosis. Nevertheless, the clear demonstration of an infundibular stenosis would sway the diagnosis toward tetralogy of Fallot.

4. Phonocardiogram shows a diamond-shape systolic murmur with most of the murmur early in systole or ending before a second sound that is single or narrowly split.

Although every one of these distinctions is important, exceptions to each have been found. Consequently, no single criterion may be taken as conclusive, but if all are present, the diagnosis of tetralogy of Fallot may be made with reasonable confidence.

These differentiations between the two lesions are based to a large extent on cardiac catheterization and its ancillary technics. It is not implied that cardiac catheterization is necessary in all instances to make the distinction with assurance; in many, if not most, clinical differentiation is easy.

Summary

Since May 1957 cardiac catheterization has been carried out in 46 patients with pulmonic stenosis and an intact ventricular septum (pulmonic stenosis) and 42 patients with pulmonic stenosis and a right-to-left shunt through a septal defect (tetralogy of Fallot).

Right atrial pressures were usually higher in pulmonic stenosis. Average pulmonary arterial and left atrial mean pressures were similar in the 2 groups, as were the pulmonary blood flows.

Although significant differences between right ventricular and systemic arterial systolic pressures may be demonstrated in tetralogy of Fallot, simultaneous right ventricular and left ventricular or aortic systolic pressures were always within a few mm. Hg of each other.

The postectopic right ventricular systolic pressure was always at least 10 mm. Hg above its previous level in pulmonic stenosis, whereas in tetralogy of Fallot it almost never exceeded its previous level by more than 10 mm. Hg.

All patients with tetralogy of Fallot had flat-topped right ventricular pressure curves, whereas 31 of 46 patients with pulmonic stenosis had triangular right ventricular pressure curves.

The phonocardiogram was found to be among the most useful tools in differentiating the 2 groups. Auscultatory phenomena of severe pulmonic stenosis with a widely split second heart sound, late crescendic diamond-shaped systolic murmur, and persistence of this murmur beyond the sound of aortic closure differed strongly from tetralogy of Fallot of equal severity.

At cardiac catheterization proof of the presence of a ventricular septal defect may be gained by passing the catheter through it. If this is not done, the presence of a ventricular septal defect may be strongly inferred if the right ventricular pressure curve has almost parallel sides and a flat or rounded top, if the right ventricular systolic pressure is near that in the systemic circulation, and if it does not rise after ectopic beats more than 10 mm. Hg above its previous level. For greater certainty in diagnosis indicator-dilution curves or angiocardiography should be done.

The accurate preoperative diagnosis of the presence or absence of a ventricular septal defect is extremely important, for at open-heart operation it is essential not to miss the ventricular septal defect after completely reliev-

ing the obstruction to right ventricular outflow; it is just as important not to do unnecessary right ventriculotomies.

Summario in Interlingua

Depost maio 1957, catheterismo cardiac esseva effectuate in 46 patientes con stenosis pulmonic e un intacte septo ventricular (stenosis pulmonic) e in 42 patientes con stenosis pulmonic e un derivation dextero-sinistre per un defecto septal (tetralogia de Fallot).

Le tension dextero-atrial esseva usualmente plus alte in le casos de stenosis pulmonic. Le valores medie del tension pulmono-arterial e del tension medie sinistro-atrial esseva simile in le 2 gruppos. Le mesmo valeva pro le fluxo de sanguine pulmonar.

Ben que significative differentias inter le tensiones systolic dextero-ventricular e systemo-arterial pote esser demonstrate in tetralogia de Fallot, le mesurationes simultanee del tensiones systolic dextero-ventricular e sinistro-ventricular o aortic differeva nunquam per plus que alicun mm de Hg.

Le postectopic tension systolic dextero-ventricular esseva semper al minus 10 mm de Hg supro su previe nivello in le casos de stenosis pulmonic durante que in le casos de tetralogia de Fallot, illo quasi nunquam excedeva su previe nivello per plus que 10 mm de Hg.

Omne le patientes con tetralogia de Fallot habeva curvas de tension dextero-ventricular a culmines platte, durante que 31 del 46 patientes con stenosis pulmonic habeva curvas triangular de tension dextero-ventricular.

Esseva trovate que le phonocardiogramma es inter le plus utile medios pro le differentiation del 2 conditiones. Le phenomenos auscultatori de sever stenosis pulmonic—un extensemente findite secunde sono cardiac, un tardive e crescendic murmure systolic de configuration rhombiforme, e le persistentia de iste murmure in ultra del sono del clausion aortic—differeva marcatemente ab illos de tetralogia de Fallot del mesme grado de severitate.

Catheterismo cardiac permitte provar le presentia de un defecto ventriculo-septal per passar le catheter a transverso ille defecto. Si isto non es facite, le presentia de un defecto ventriculo-septal pote esser suspicite con alte grados de probabilitate si le curva de tension dextero-ventricular ha lateres que es quasi parallel e culmines que es platte o ronde, si le tension systolic dextero-ventricular es in le vicinitate del tension del circulation systemic, e si illo non monta post pulsos ectopic per plus que 10 mm de Hg in supra de su previe nivello. Pro obtener un plus alte grado de certitude in le diagnose, curvas de dilution de indicator o datos angiocardiographic debe esser obtenite.

Le accurate diagnose preoperatori de presentia o absentia de defecto ventriculo-septal es extrememente importante, proque in le chirurgia cardiac aperte on non debe negliger le defecto ventriculo-septal post completemente alleviar le obstruction al effluxo dextero-ventricular, sed on etiam debe evitar le ventriculotomia dextere si un tal non es necessari.

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The perplexity was further increased by the existence of murmurs independent of valvular disease, and accompanying both hypertrophy with dilatation, and a nervous action of the heart without any organic lesion whatever. These murmurs Laennec attributed to a wrong cause: viz. to the sound of the muscular contraction, instead of to the modified motion of the fluid; which I presume to consider the true cause.—J. HOPE, M.D. *Diseases of the Heart and Great Vessels.* London, William Kidd, 1832, p. 15.

Pulmonic Stenosis, Ventricular Septal Defect, and Right Ventricular Pressure above Systemic Level

By J. I. E. Hoffman, M.D., Abraham M. Rudolph, M.D., Alexander S. Nadas, M.D., and Robert E. Gross, M.D.

IT IS USUALLY possible to distinguish pulmonic stenosis with an intact ventricular septum (designated as pulmonic stenosis) from pulmonic stenosis with a right-to-left shunt through a ventricular septal defect (tetralogy of Fallot) by routine clinical, electrocardiographic, and radiologic examination.[1-3] If the diagnosis is still uncertain, it can as a rule be made by phonocardiography and cardiac catheterization,[4] particularly if there is very severe pulmonic stenosis with an intact ventricular septum. Characteristically in severe pulmonic stenosis the right ventricular systolic pressure is much higher than in the systemic circulation and rises still higher after ectopic beats; the right ventricular pressure tracing is triangular; and right ventricular systole is prolonged so that on phonocardiography the second heart sound is widely split and the systolic murmur passes beyond aortic valve closure. Unfortunately these commonly accepted criteria may be unreliable. In this paper 10 patients are reported who, although meeting most or all of these criteria for the diagnosis of severe pulmonic stenosis (especially with systolic pressures much higher in the right ventricle than in the systemic arteries), nevertheless were proved later to have an associated ventricular septal defect with a right-to-left shunt. An attempt is made to indicate how even under these circumstances a correct preoperative diagnosis may be made.

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Dr. Rudolph is an Established Investigator of the American Heart Association.

Material and Methods

These 10 patients were admitted to the Children's Medical Center for investigation and operation, and all but 1 were seen after June 1957. Cardiac catheterizations as described previously from this laboratory[5] were done in all, and phonocardiograms were taken with a Sanborn Twin-Beam photographic recorder.

Results

Clinically all of these patients had one or more signs suggestive of valvular pulmonic stenosis with an intact ventricular septum. There were large "a" waves in the jugular venous pulse in 4; the systolic thrill in 7 and the stenotic systolic murmur in 8 were maximal at the second or third left intercostal space; the second heart sound was thought to be widely split in 4; and 2 with clinically severe pulmonic stenosis had no cyanosis. The electrocardiogram showed P pulmonale in 6 and marked right ventricular hypertrophy in all 10; the R waves in lead V_1 were 20 to 30 mm. high in 5 and over 30 mm. high in 4. On x-ray, 8 had cardiac enlargement (marked in 4) and 4 had what was interpreted as poststenotic dilatation of the pulmonary artery. Any of these signs may be found in an otherwise classical tetralogy of Fallot but all of them individually or together favor severe valvular pulmonic stenosis with an intact ventricular septum and high right atrial and ventricular pressures.

Cardiac catheterization supported the diagnosis initially when right atrial pressures over 10 mm. Hg were found in 7, and in all 10 the right ventricular systolic pressure was above systemic levels. In 1 the right ventricular systolic pressure of 125 mm. Hg was only 15 mm. Hg above that in the brachial artery, but in all the others it ranged from 150 to 250 mm. Hg, with a systolic gradient between right

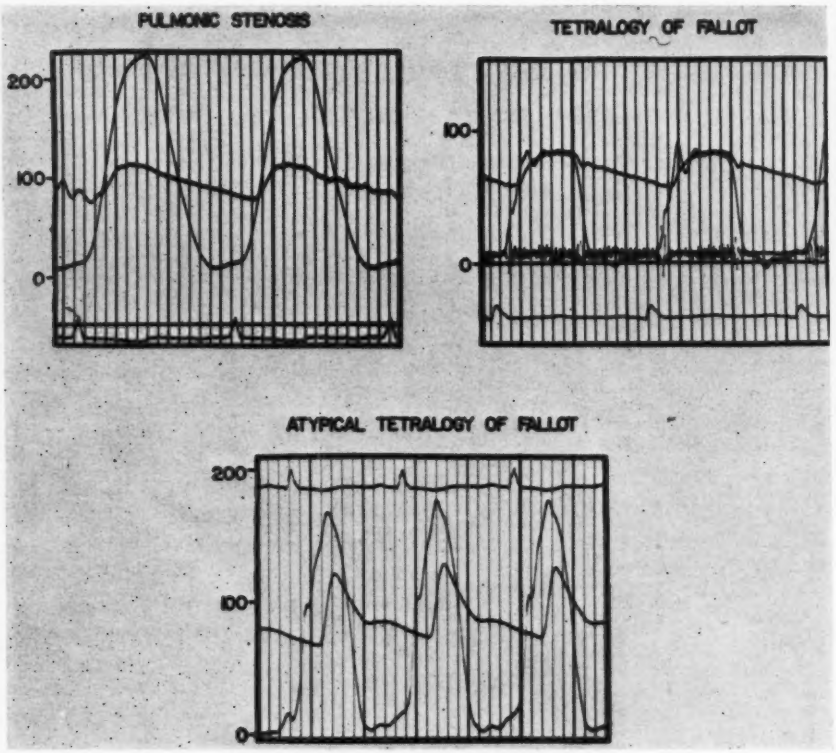

Figure 1

Right ventricular pressure curves with simultaneous aortic pressure curves (top) *and brachial artery pressure curve* (bottom).

ventricle and systemic artery of 35 to 120 mm. Hg. An intact ventricular septum was further suggested when in 7 the right ventricular systolic pressure rose 15 to 40 mm. Hg above its previous level after a premature beat; in the other 3 right ventricular pressures were not recorded during premature beats.

The shape of the right ventricular pressure curve was roughly triangular (fig. 1) as found in pulmonic stenosis but not in tetralogy of Fallot. In 6 the ratio of the curve width 20 per cent above the midsystolic pressure to the width 20 per cent below it was small and well under 0.70, the lower limit of the range established for tetralogy of Fallot;[4] in the other 4 the value of the ratio fell in the zone common to both groups.

Despite this cumulative evidence of severe pulmonic stenosis all 10 patients had ventricular septal defects with right-to-left shunts. This was proved preoperatively in 2 by passing the catheter from right ventricle to aorta through the defect. In these 2 as well as in 5 other patients, indicator-dilution curves showed a right-to-left shunt at the ventricular level; in 2 of these the shunt was shown by injections made into the body of the right ventricle but not into the infundibulum. Indicator-dilution curves were also done in 2 of the remaining 3 patients and showed a right-to-left shunt at the atrial but not at the ventricular level. The magnitude of these right-to-left shunts varied widely, so that systemic arterial oxygen saturation ranged from 47 to 93 per cent; in 6 of the 10 it was between 80 and 89 per cent.

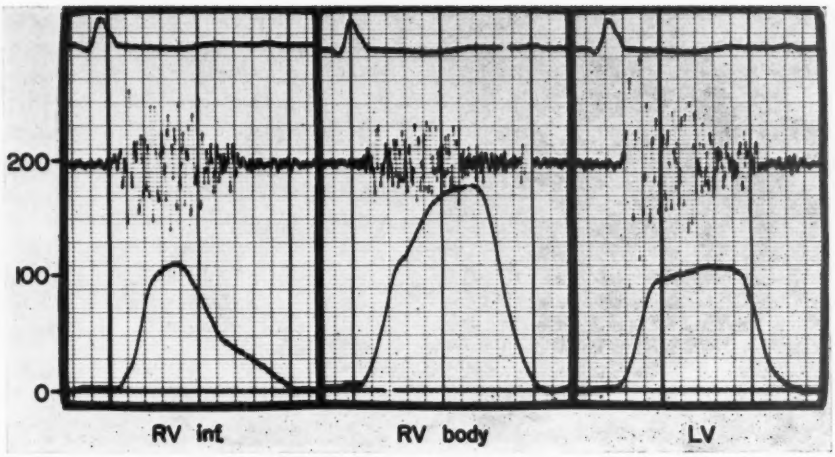

Figure 2

Electrocardiograms (top), *external phonocardiograms* (center), *and pressure curves* (bottom) *to show that the notch in the ascending limb of the right ventricular body pressure curve occurs at the level of the systolic pressure in the right ventricular infundibulum or the left ventricle. Note also the early diamond-shaped murmur.*

There was a notch or abrupt change in direction of the ascending limb of the right ventricular pressure curve in 7; this notch always occurred about the level of the systemic systolic pressure, and was also near the systolic pressure in the infundibular chamber in 3 (fig. 2).

At cardiac catheterization the site of the stenosis was judged to be definitely valvular and infundibular in 3, valvular and possibly infundibular in 3, and infundibular alone in 2; in 2 the pulmonary artery was not entered but cineangiogram in 1 showed an infundibular chamber. Four showed a zone of negative pressure as the catheter tip passed from the pulmonary artery to and through the stenotic area (Bernouilli effect) and 1 of these was a patient with pure infundibular stenosis.

Phonocardiograms were taken in all these patients (fig. 3). The first heart sound was normally split in all and was either normal or reduced in intensity. Five had a systolic click 0.08 to 0.14 second after the beginning of the first heart sound; in 3 this click was louder in expiration, in 1 it increased during inspiration and in 1 did not change in intensity with respiration. Four had soft third heart sounds and 8 had fourth heart sounds of slight to marked intensity.

Identification of the 2 components of the second heart sound may be difficult if pulmonic closure is very soft and is obscured by the systolic murmur passing beyond the aortic closing sound, and if the absence of a suitable external reference makes it difficult to be sure that a small vibration does indeed represent pulmonic closure. In 6 the second heart sound was regarded as single or narrowly split (up to 0.03 second) and in 4 it was probably widely split (0.06 to 0.10 second).

The systolic murmur was diamond-shaped in 9 and decrescendo in 1 but had many variations in configuration. In all it began immediately or shortly after the first heart sound, which was always distinct, and it began before the systolic click in the 5 who had it. In the most severely affected patient there was a soft decrescendo systolic murmur ending at or before the single second heart sound (fig. 3*C*). In 3 the systolic murmur increased rapidly to a maximum in the first quarter of systole, remained at this intensity for a short time, and then decreased to end at or beyond the second heart sound (fig. 3*D-F*). Four others (fig. 3*G-*

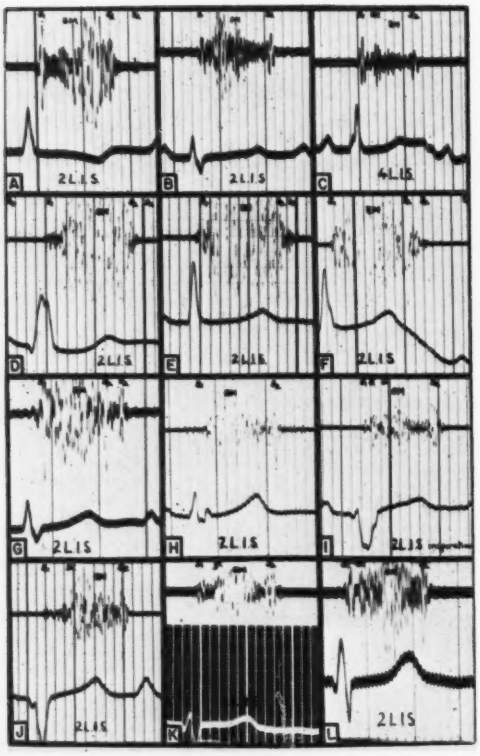

Figure 3

Phonocardiograms. A. Typical pulmonic stenosis. B. Typical tetralogy of Fallot. C-L. Patients in this series. 2LIS, second left intercostal space; 4LIS, fourth left intercostal space; S_1, first heart sound; S_2, second heart sound; S_4, fourth heart sound; SM, systolic murmur; SC, systolic click.

J) had more typical diamond-shaped systolic murmurs that nevertheless were maximal early in systole, so that they resembled a kite lying on its side with its tail pointing toward the right; 2 of these murmurs ended at, and 2 ended after, the second heart sound. Finally, 2 had symmetrical diamond-shaped systolic murmurs with their maxima in midsystole, but 1 ended well before the second heart sound and the other at or just beyond it (fig. 3*K* and *L*); in each, some complexes did have early diamond-shaped murmurs.

Anatomic details were noted at open-heart operation in 9. All had infundibular stenosis, which was suggested by the low intravalvular position of the thrill and in at least 3 by an indentation in the right ventricular outflow tract some distance below the pulmonary valve; in addition there were 4 with valvular stenosis and thrills in the pulmonary artery. One patient had a corrected transposition with the right ventricle anteriorly and on the (patient's) left and the pulmonary artery emerging to the right of and posterior to the aorta. This patient had what was almost a single ventricle with the lower three quarters of the ventricular septum missing and with marked muscular hypertrophy below the pulmonary and aortic valves. All the others had high membranous ventricular septal defects; one of these was recorded as being "quite small," 3 had areas of 0.5 to 1.0 cm.^{2}, and 4 had areas of 1.5 to 2.0 cm.^{2}

Discussion

In 1951 Soulié, Joly, Carlotti, and Sicot[6] described right ventricular systolic pressures above systemic levels in 3 of 22 patients with tetralogy of Fallot. McGoon and Kirklin,[7] in reporting 32 patients with "an essentially intact ventricular septum," mentioned 1 patient with a ventricular septal defect and an abnormally high right ventricular pressure. In our series 9 of 10 patients were seen in a period when about 35 patients with pulmonic stenosis and about 35 with tetralogy of Fallot were catheterized. In the same period some with tetralogy of Fallot and a few with pulmonic stenosis were operated on without cardiac catheterization and many others in both groups were seen but not operated on. There may be still more patients with this syndrome who have been diagnosed as pulmonic stenosis and in whom the error has not yet been discovered, but even without them this variant of tetralogy of Fallot seems to be relatively common.

Physiologic Mechanism

In tetralogy of Fallot there is usually rapid pressure equilibrium across the ventricular septal defect so that systolic pressures in the right and left ventricles and aorta are similar and rise slightly or not at all after ectopic beats, right and left ventricular pressure

tracings have similar shapes with almost parallel sides and flat or rounded tops, and ventricular ejection ends at about the same time in two ventricles. Consequently the second heart sound is single or narrowly split and the systolic murmur does not pass beyond aortic valve closure.[4] By contrast, all 10 patients reported here acted as if the ventricular septum were intact, in that the right ventricle could generate a systolic pressure higher than that in the systemic circulation and could further elevate this after ectopic beats. In a group of patients with tetralogy of Fallot studied in this laboratory, 30 mm. Hg was about the maximum difference found between right ventricular and systemic arterial systolic pressures when systolic pressures in the right ventricle and aorta were almost identical, so that differences greater than this probably indicate some failure of pressure equilibration between the two ventricles. In the one patient with a systolic gradient of only 15 mm. Hg between right ventricle and systemic artery evidence of an intact septum was inferred from a 25 mm. Hg rise in right ventricular systolic pressure after ectopic beats and from the demonstration of a widely split second heart sound with the systolic murmur ending after aortic valve closure. In this patient, too, as well as in 5 others, the shape of the right ventricular pressure curves was typical of pulmonic stenosis.

This failure of rapid pressure equilibration across the ventricular septal defect suggests that the ventricular septum may be functionally intact during part or all of systole, and the following possible reasons based on our experience with these 10 patients may be advanced:

1. The defect may be occluded by the septal leaflet of the tricuspid valve. In one patient at autopsy this leaflet had an anomalous origin from the margin of the ventricular septal defect (fig. 4) and could conceivably have obstructed it during systole. In another patient at operation the tricuspid valve leaflet was found to be partly adherent to the rim of the defect.

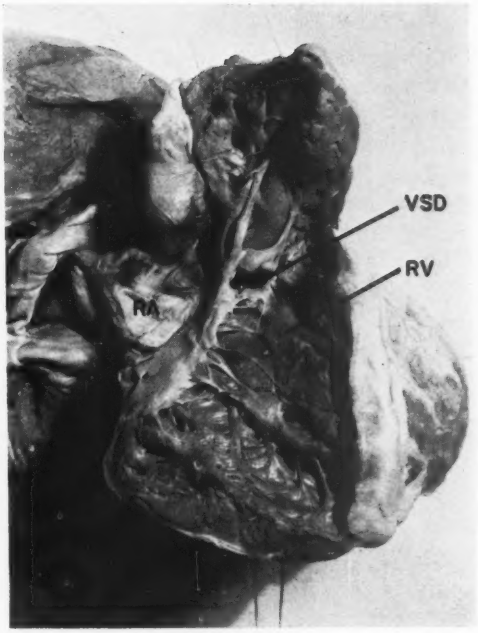

Figure 4

Right ventricle showing anomalous origin of a tricuspid valve leaflet from the margin of the ventricular septal defect. RA, right atrium; RV, right ventricle; VSD, ventricular septal defect.

2. If the defect is very small then pressure equilibration across it could be delayed. Soulié and his colleagues[6] invoked this explanation in 3 patients with this syndrome who had minimal right-to-left shunts, and McCord, van Elk, and Blount[8] found a defect 5 mm. in diameter in their patient. Only 2 patients in our series had small defects, though 1 of these had an arterial oxygen saturation of 82 per cent.

3. If the defect is situated in the infundibular chamber, it may become isolated from the body of the right ventricle during systole and thus may not be able to decompress it. This may have occurred in 1 patient reported by McGoon and Kirklin[7] but was not found in our series.

4. It is possible that the ventricular septal defect could be occluded by contraction of the hypertrophied muscle of the septum and the crista supraventricularis, so that toward

the end of systole the ventricular septum would be effectively closed. Recently, proof of this hypothesis was obtained in one of these patients at operation. The right ventricle was opened while the circulation was maintained by the pump oxygenator; the heart was not stopped. With each contraction the ventricular septal defect was squeezed closed by the hypertrophied muscle around it and the infundibular chamber was cut off from the body of the right ventricle.

One or both of these events might have caused the notch in the ascending limit of the right ventricular pressure tracing in this patient and 6 others. A similar notch was noted only once in pulmonic stenosis in a patient with marked infundibular stenosis.

Preoperative Diagnosis

Accurate preoperative diagnosis of this lesion is essential in indicating the need for surgical repair with extracorporeal circulation rather than with hypothermia and in making right ventriculotomy mandatory. Phonocardiography was of great help in suggesting that these patients did not have pulmonic stenosis with an intact ventricular septum inasmuch as (a) the systolic murmur was maximal early in systole, whether or not it passed beyond aortic valve closure or (b) the systolic murmur ended before a single or closely split second heart sound, whether or not the murmur was maximal early in systole. It is true that in mild pulmonic stenosis right ventricular ejection may not be prolonged so that the systolic murmur may be maximal in midsystole and end at the aortic component of a normally split second heart sound, but these patients will not show the features of marked right ventricular hypertrophy.

These phonocardiographic criteria may not hold if there is pulmonic stenosis and ventricular inversion (corrected transposition). Three patients with this syndrome have been seen with phonocardiograms typical of tetralogy of Fallot but with no evidence of an associated ventricular septal defect on cardiac catheterization. The diagnosis has not yet been proved at operation, and until then phonocardiograms in this syndrome should be interpreted with caution.

If after clinical, radiologic, and phonocardiographic examination cardiac catheterization is required, it is obvious that in patients with pulmonic stenosis complete reliance to exclude an associated ventricular septal defect cannot be placed on a high right ventricular systolic pressure that rises further after ectopic beats and on a triangular right ventricular pressure curve. The only direct preoperative demonstration of this defect is the passage of the catheter through it from the right ventricle to the aorta; failing this, indicator-dilution studies or angiocardiography should always be done. The site of injection of the indicator or radiopaque dye is important, for if it is injected into the infundibulum or into a stream that does not pass through the defect, the right-to-left ventricular shunt may not be revealed. This happened in 2 of our patients with arterial oxygen saturations of 89 and 93 per cent, in both of whom right atrial injection showed a right-to-left shunt. Failure to demonstrate a right-to-left ventricular shunt by these technics, especially when the arterial oxygen saturation is near normal, is thus not unequivocal evidence of its absence. Another possible source of error occurs with marked tricuspid regurgitation and a right-to-left atrial shunt, for then indicator injected into the body of the right ventricle might be swept back into the right atrium and then across to the left side; a good angiocardiogram should help to avoid this error and has the additional advantage of demonstrating the anatomy of the outflow tract of the right ventricle.

Summary

Ten patients with pulmonic stenosis are reported who, despite having right ventricular systolic pressures much above systemic levels, had ventricular septal defects proved at operation in 9 and suggested by indicator-dilution curves in the other.

Because of the high right ventricular systolic pressures these patients had clinical and electrocardiographic evidence of marked right ventricular hypertrophy and were initially

thought to have severe pulmonic stenosis with an intact ventricular septum.

One patient had an almost single ventricle with pulmonic and aortic stenosis.

In all the others the right ventricular systolic pressure failed to equilibrate with pressures in the systemic circulation. In 2 patients this was probably due to obstruction of the ventricular septal defect by the septal leaflet of the tricuspid valve. In the others the suggestion that the ventricular septal defect was closed off during systole by muscular contraction was confirmed in 1 patient at operation.

This syndrome has been reported in other series and may occur in as many as 5 to 10 per cent of patients diagnosed as having severe pulmonic stenosis.

It is important to know before operation whether or not there is a ventricular septal defect associated with the pulmonic stenosis, for this influences the decision about doing a right ventriculotomy.

The preoperative diagnosis of this variant of tetralogy of Fallot may be made by phonocardiography and cardiac catheterization.

Summario in Interlingua

Es reportate dece casos de stenosis pulmonic in que—in despecto de nivellos del tension systolic dextero-ventricular multo supra le nivellos del tension in le circulation major—le presentia de defectos ventriculo-septal esseva demonstrate al operation (9 casos) o suggerite per le curvas del dilution de un indicator (1 caso).

In consequentia del alte tensiones systolic dextero-ventricular, iste patientes manifestava evidentia clinic e electrocardiographic de marcate grados de hypertrophia dextero-ventricular e esseva considerate initialmente como suffrente de sever stenosis pulmonic con intacte septo ventricular.

Un del patientes habeva quasi un sol ventriculo con stenosis pulmonic e aortic.

In omne le altere casos, le tension systolic dextero-ventricular non se equilibrava con le tensiones in le circulation systemic. In 2 patientes isto esseva probabilemente le effecto del obstruction del defecto ventriculo-septal per le lobo septal del valvula tricuspidal. Quanto al alteres, il esseva suspicite que le defecto ventriculo-septal esseva claudite durante le systole per un contraction muscular, e iste suspicion poteva esser confirmate in un caso al operation.

Iste syndrome ha essite reportate per altere autores in altere series de casos e occurre possibilemente in usque a 5 o 10 pro cento del casos diagnosticate como sever stenosis pulmonic.

Es importante saper ante le intervention chirurgic si o non le patiente ha un defecto ventricular-septal in association con su stenosis pulmonic, proque isto exerce un influentia super le decision de si o non un ventriculotomia dextere debe esser effectuate.

Le diagnose pre-chirurgic de iste variente del tetralogia de Fallot pote esser facite per phonocardiographia e catheterismo cardiac.

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Cardiac Enlargement in Chronic Severe Anemia

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ALTHOUGH cardiac enlargement in patients with chronic severe anemia was reported earlier in necropsy studies,[1, 2] it was first demonstrated roentgenologically by Ball,[3] who also showed that enlargement disappeared with correction of anemia. Enlargement has been attributed to dilatation or hypertrophy associated with dilatation.[3-7] Experimentally Ludke and Schuller[8] demonstrated cardiac dilatation in dogs after producing anemia. Cardiac hypertrophy also has been described in experimentally produced anemia.[9-12] Paplanus et al.,[12] in a recent study in which severe anemia was produced in dogs by repeated venesections, demonstrated that anemia per se can cause cardiac hypertrophy. The mechanism of cardiac enlargement and its relationship to hemoglobin level and other factors are uncertain. In this country severe curable anemias associated with a high incidence of cardiac enlargement and of complicating congestive failure are frequently encountered. It was thought therefore that study of a large series of patients until the anemia was cured may prove of value in assessing the nature of cardiac enlargement and its relation to various factors. The purpose of this communication is to report the results of such a study in 150 patients.

Material and Methods

One hundred and fifty patients with anemia of at least 3 months' duration and hemoglobin levels of less than 8 Gm. per 100 ml. were studied. Only patients who were hospitalized until the anemia was cured and in whom no evidence of any other cardiovascular disease could be detected after cure of anemia were included in the study. There were 93 male and 57 female patients, with ages varying from 10 to 55 years (table 1). The hemoglobin level varied from 1 to 8 Gm., with an average of 3.5 Gm. Anemia was due to chronic malaria in 80 cases, ankylostomiasis in 32, chronic dysentery in 11, bleeding hemorrhoids in 8, and uterine bleeding in 8, and was of undetermined etiology in 11 cases. Duration of anemia varied from 3 months to 5 years, with an average of 13 months. Congestive cardiac failure was considered to be present in 43 patients, of whom 24 were female.

Fluoroscopic examination of the heart chambers, direct measurement of the venous pressure, and estimation of circulation time by magnesium sulfate method were done on admission. Chest roentgenograms were taken usually twice, on admission and after cure of anemia. The heart was considered enlarged if the cardiothoracic ratio was more than 50 per cent. Duration of anemia was difficult to ascertain accurately. For the purpose of this study the first appearance of symptoms, such as weakness and fatigability, exertional dyspnea, palpitation, and anorexia, was considered; the actual duration of anemia was probably much longer than estimated. Heart failure was diagnosed after careful evaluation of edema, hepatomegaly, orthopnea, venous pressure, circulation time, and rapidity of regression of hepatic and cardiac enlargement, because many of these manifestations may be present without failure. Patients were divided into 3 arbitrary groups according to hemoglobin levels; less than 3 Gm., 3 to 5 Gm., and more than 5 Gm. per 100 ml. Statistical evaluation of the data was done by the chi-square test.

Apart from treatment of the etiologic factor, routine therapy included administration of saccharated oxide of iron intravenously and ferrous sulfate and multivitamin pills orally. Because of the difficulty of obtaining donors, blood transfusion was given initially mostly to patients with hemoglobin of less than 3 Gm. per 100 ml. or with heart failure.

Results

Enlargement of the cardiac shadow was found in 120 patients, including all the 43 patients with cardiac failure; the cardiothoracic ratio in these patients varied from 51 to 82 per cent, with an average of 55 per cent.

The relation of the cardiothoracic ratio to the hemoglobin level and heart failure is given in table 2. The relation of failure, enlargement, and cardiothoracic ratio of more than 55 per cent to hemoglobin level and sex is given in table 3. A highly significant difference was found in the incidence of cardiac

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Table 1

Age and Sex Distribution

Age (yr.)	Male	Female	Total
0-20	39	15	54
1-30	31	25	56
1-40	9	10	19
1-50	13	4	17
1-55	1	3	4
Total	93	57	150

Table 2

Relation of Cardiothoracic Ratio to Hemoglobin Level and Failure on Admission

Hgb. Gm./%	Total cases	No. with Cardiothoracic ratio % up to 55	56-65	66-75	>75	Mean Cardiothoracic ratio %
<3	61	30	20	7	4	56 ± 7.2
3-5	66	48	15	3	0	53 ± 6.4
>5	23	22	1	0	0	50 ± 4.1
Without failure	107	90	16	1	0	50 ± 5.7
With failure	43	10	20	9	4	62 ± 8
Total	150	100	36	10	4	55 ± 8

failure ($\chi^2 = 21.11$; $p<.001$) as well as in the number of patients with a cardiothoracic ratio of more than 55 per cent ($\chi^2 = 18.06$; $p<.001$) in the 3 hemoglobin groups, but no significant difference was found in the incidence of enlargement. Of the 23 patients with more than 5 Gm. of hemoglobin, none had heart failure and only 1 had a cardiothoracic ratio of more than 55 per cent. Of 107 patients without failure, 90 had a cardiothoracic ratio up to 55 per cent and only 1 had more than 65 per cent. A cardiothoracic ratio up to 55 per cent was, however, seen in 10 patients with failure and in 31 patients with less than 3 Gm. of hemoglobin.

The incidence of enlargement was nearly equal in male and female patients. Incidence of heart failure was, however, significantly greater in women ($\chi^2 = 8.02$; $.003<p<.005$). This appeared to be largely responsible for the greater degree of cardiac enlargement in women. The average cardiothoracic ratios among cases with enlarged heart were 59 and 55 per cent for female and male patients, respectively. Cardiothoracic ratios of more than 55 and 65 per cent, respectively, were found in 29 (51 per cent) and 10 (17 per cent) women and 21 (22 per cent) and 4 (4 per cent) men.

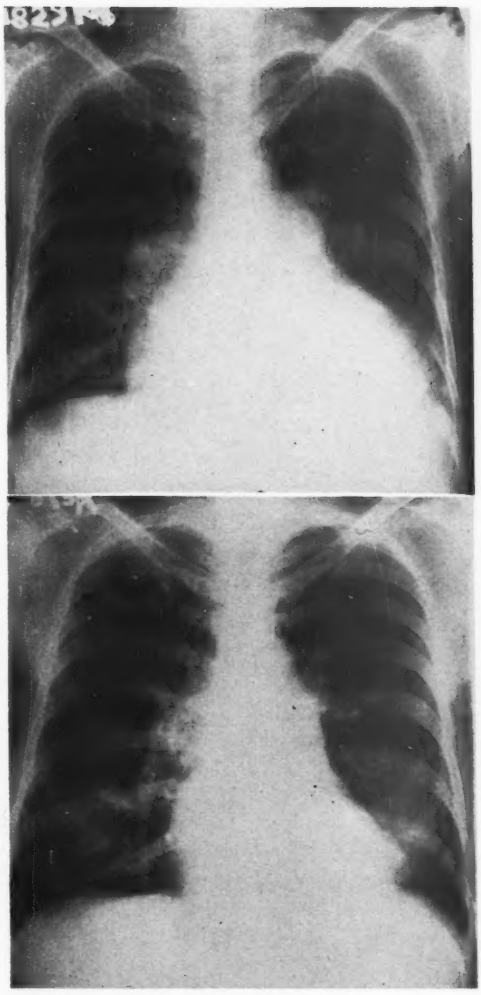

Figure 1

Roentgenograms of a 35-year-old woman with cardiac failure. Top. *Typical mitralized configuration (cardiothoracic ratio 70 per cent).* Bottom. *Slight cardiac enlargement (cardiothoracic ratio 52 per cent) after cure of anemia.*

The age of the patient and the etiologic factor or the duration of anemia (table 4) were

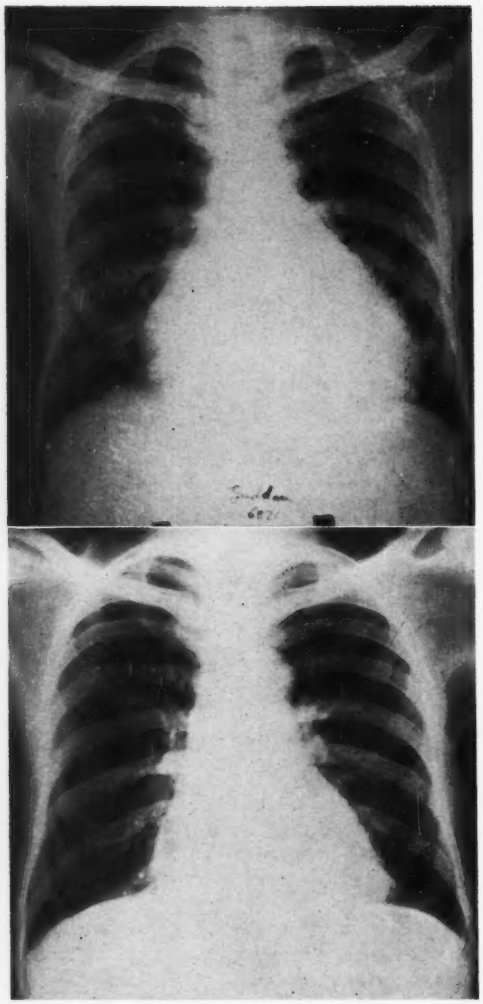

Figure 2

Roentgenograms of a 45-year-old man with cardiac failure and pericardial effusion. Top. *Pear-shaped cardiac shadow (cardiothoracic ratio 68 per cent).* Bottom. *Persistent enlargement (cardiothoracic ratio 54 per cent) 14 weeks later and 5 weeks after cure of anemia.*

not found to have any significant relation to the incidence of cardiac enlargement and failure.

The type of cardiac enlargement was generalized in 43 cases, predominantly left ventricular in 31, predominantly right ventricular with prominent conus or pulmonary artery

Table 3

Relation of Cardiac Failure and Enlargement to Hemoglobin Level and Sex

Hgb. Gm./%	Total cases	No. with failure	No. with enlargement	Cardiothoracic ratio >55%
<3	61	29 (48%)	54 (88%)	31 (50%)
3-5	66	14 (21%)	50 (75%)	18 (27%)
>5	23	—	16 (70%)	1 (4%)
Sex				
M	93	19 (20%)	73 (78%)	21 (22%)
F	57	24 (42%)	47 (82%)	29 (51%)

Table 4

Relation of Cardiac Failure and Enlargement to Duration of Anemia

Duration (yr.)	Total cases	Per cent failure	Per cent enlargement
<1	95	23	75
1-3	42	40	88
>3	13	30	92

(fig. 1) in 43, and pear-shaped (figs. 2 and 3) in 3 cases. The present series confirmed the previous observation in a smaller series[13] that right and left ventricular types of enlargement were usually seen in cases with and without tachycardia, respectively. In 2 cases with pear-shaped cardiac silhouette, on paracentesis, 100 and 150 ml., respectively, of clear straw-colored fluid were aspirated from the pericardial sac; the enlarged silhouette was chiefly due to cardiac enlargement and only to a small extent to pericardial effusion. Both cases had congestive failure. In another case paramediastinal effusion on the right side simulated marked dilatation of the right atrium.[14]

Cardiac size decreased rapidly with correction of anemia and relief of heart failure; it returned to normal (fig. 4) in 92 of the 120 cases with enlargement on admission. Some enlargement, however, persisted after cure of the anemia in 28 cases (figs. 1 to 3). The cardiothoracic ratio after cure in these cases ranged between 52 and 58 per cent, with an average of 54 per cent. Significant difference was found in the incidence of persistent enlargement (table 5) in cases with and without failure ($\chi^2 = 11.93$; $p<.001$) and

Table 5

Relation of Persistent Enlargement to Hemoglobin Level and Failure

Hgb. Gm./%	Enlargement	
	Total cases	Per cent persistence
<3	54	35
3-5	50	14
>5	16	13
Without failure	77	13
With failure	43	42
Total	120	23

in the 3 hemoglobin groups ($\chi^2 = 7.13$; $.018 < p < .030$), particularly in those with less than 3 Gm. and more than 3 Gm. ($\chi^2 = 7.42$; $.005 < p < .008$). The cardiothoracic ratio on admission was more than 60 per cent in 25 and more than 55 per cent in 27 of the 28 cases, and 18 of them had heart failure.

Discussion

The high incidence of cardiac enlargement in the present series is apparently due to the greater intensity of anemia in our patients. Within the scope of this study the actual incidence of enlargement was not found to have significant relation to age and sex of the patient, the duration or the etiologic factor of anemia and the hemoglobin level. This suggests that enlargement is very likely to occur when the hemoglobin level falls below 8 Gm. per cent and that it is due to the anemia per se. There was no consistent relation between the cardiac size and the hemoglobin level on admission. Evaluation of the data, however, revealed a significant difference in the cardiothoracic ratio and incidence of cardiac failure at various hemoglobin levels. Cardiac failure as well as considerable enlargement was seen only in cases with hemoglobin values of 5 Gm. or less, and the latter was mostly associated with failure. In two other series of heart failure due to anemia[13, 15] the hemoglobin was less than 5 Gm. in all the cases.

An interesting feature was a significantly larger cardiac size and increased incidence of cardiac failure in female than in male patients, while there was no significant difference in the incidence of enlargement. It has been commented upon that exertion during the anemic state plays an important role in the production of cardiac enlargement and causation of failure.[16] In our series women

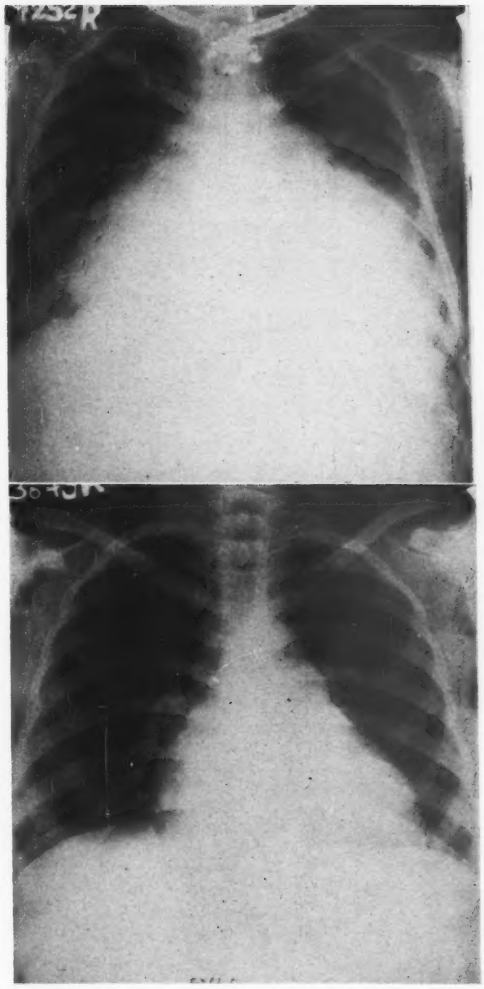

Figure 3

Roentgenograms of a 17-year-old girl with cardiac failure. Top. *Considerable cardiac enlargement (cardiothoracic ratio 82 per cent).* Bottom. *Persistent enlargement (cardiothoracic ratio 58 per cent) 15 weeks later and 6 weeks after cure of anemia.*

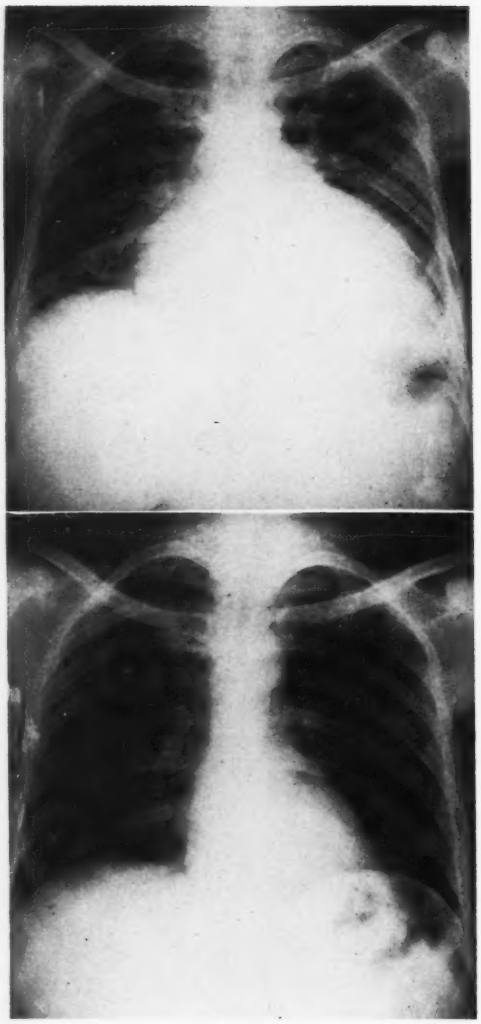

Figure 4

Roentgenograms of a 25-year-old man with cardiac failure. Top. *Considerable cardiac enlargement (cardiothoracic ratio 70 per cent).* Bottom. *Normal size heart (cardiothoracic ratio 45 per cent) 8 weeks later.*

were mostly housewives doing light manual work while men were mostly laborers or cultivators doing heavy manual work. It is conceivable that men, because of their heavy work as wage earners, notice symptoms and seek treatment earlier. Their heart size even when heart failure develops would therefore be comparatively less than women, who usually seek treatment only when they are incapacitated because of the severity of anemia or heart failure. This view is supported by the finding that of the 10 patients with failure and a cardiothoracic ratio of less than 55 per cent, 8 were men.

With correction of anemia the heart size diminished rapidly; it returned to normal in 77 per cent of the cases with initial enlargement. Enlargement in these cases can therefore be attributed to dilatation alone. The maximum cardiothoracic ratio among these cases was as high as 70 per cent (fig. 4), showing the extent to which the heart can dilate and yet return to a normal size. This return occurred usually when the hemoglobin level rose to more than 12 Gm. per 100 ml. and within a period of 4 to 10 weeks.

In 23 per cent of the cases, the heart remained enlarged despite cure of the anemia. The maximum cardiothoracic ratio after cure in these cases was 58 per cent, showing that cardiac enlargement above this size in all our cases was due to dilatation. It is realized that in some of the cases the heart size may still return to normal in the course of time. Use of the cardiothoracic ratio as an index of enlargement is only a rough guide and may sometimes be inaccurate, since the relationship between the diameter of the heart and that of the chest varies considerably. In a control series of normal individuals in Jaipur the cardiothoracic ratio ranged between 39 and 47 per cent, with an average of 44 per cent. A cardiothoracic ratio of more than 50 per cent in our cases is therefore considered to represent definite cardiac enlargement. Instances of persistent enlargement have been reported previously.[5, 6, 17, 18] The high incidence in the present series is probably due to the greater intensity of anemia and high incidence of heart failure. Enlargement was persistent irrespective of the age of the patient (fig. 3), and there was little possibility of associated coronary artery disease being responsible for it. The possibility of vitamin or nutritional deficiency as a cause is unlikely because all the patients were given a mul

tivitamin pill including vitamin B-complex factors and a high-protein diet during the period of hospitalization.

Electrocardiographic and ballistocardiographic abnormalities have been reported to persist in some cases after cure of anemia,[19, 20] and the possibility that some dilatation may persist if the cardiac damage has been severe, with persistence of mechanical inefficiency, cannot be ruled out. It has, however, already been seen that even a markedly enlarged heart returns rapidly to normal size with cure of anemia, thus demonstrating that enlargement due to dilatation alone disappears completely. Persistent enlargement was mostly seen in cases with large hearts on admission. Furthermore, cardiac hypertrophy has been noted at necrospy in patients with anemia as well as in experimentally produced anemia. It is therefore most likely that persistent enlargement is associated with hypertrophy although this may be accompanied by some dilatation.

The presence of pericardial effusion in patients with congestive failure due to anemia has not so far been demonstrated during life in any case. In the present series effusion was demonstrated in 2 cases, both of whom recovered completely from anemia. At necropsy serous pericardial effusion in patients who died of congestive failure apparently due to pernicious anemia, and lemon-yellow hydropericardium in cases of erythroblastic anemia have been noted.[21] Soloff and Bello[22] drew attention to the difficulty in differentiating roentgenographically cardiac dilatation from pericardial effusion in patients with anemia and were the first to demonstrate effusion during life in 2 patients with anemia. The heart was normal in size in both patients, and the effusion was not due to congestive failure. It may have been due to hemopigmentary pericarditis or to redistribution of fluid within the functional body compartments.[22] Both of our cases had definite congestive failure and large hearts, and the effusion was apparently due to heart failure and not due to anemia. Some enlargement of the heart persisted after cure of anemia in both cases.

Summary

One hundred and fifty patients with chronic severe anemia were studied to determine the nature of cardiac enlargement and its relation to various factors.

Enlargement was present in 120 patients. It showed no consistent relation to the hemoglobin level on admission. A significant increase in the cardiac size and incidence of failure was observed with increased severity of anemia, and in female as compared to male patients. The incidence of enlargement showed no relation to the age and sex of the patient and the duration or the etiologic factor of anemia.

With correction of the anemia, enlargement disappeared rapidly in 92 patients, indicating that it was due to dilatation alone. Some enlargement persisted in 28 patients, and it is believed to be associated with cardiac hypertrophy.

Pericardial effusion due to heart failure in 2 patients contributed to a small extent to the enlargement of the cardiac shadow.

Acknowledgment

Our thanks are due to Dr. L. R. Sarin, Superintendent, Sawai Man Singh Hospital, for permission to publish this report, and to Dr. R. Sharma for statistical evaluation of the data.

Summario in Interlingua

Cento cinquanta patientes con formas sever de anemia chronic esseva studiate pro determinar le natura del allargamento cardiac in illes e su relation con varie factores.

Allargamento cardiac esseva presente in 120 del casos. Illo monstrava nulle uniforme relation con le nivello de hemoglobina al tempore del hospitalisation. Un significative augmento del dimensiones cardiac e del incidentia de disfallimento esseva observate con le augmento del grado de severitate del anemia e in femininas in comparation con masculos. Le incidentia del allargamento cardiac monstrava nulle relation al etate e al sexo del patientes e al duration o al factores etiologic del anemia.

Con le correction del anemia, le allargamento cardiac dispareva rapidemente in 92 patientes. Isto indicava que le condition esseva causate exclusivemente per un dilatation del corde. Un certe grado de allargamento cardiac persisteva in 28 patientes. Es opinate que isto esseva associate con hypertrophia cardiac.

Effusion pericardial causate per disfallimento car-

diac in 2 patientes contribueva in un certe basse mesura al allargamento del umbra cardiac.

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Quite characteristic of the habit of the human mind, we seem to find considerable comfort in interpreting an experience if we can find a plausible or even generally accepted cause for it. If we think we know its cause, in some measure we are at least relieved. Likewise, we take similar solace from giving it a name even when thinking about the name might raise more questions than it answers.—ALAN GREGG, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 26.

Bilateral Indirect and Direct Arterial Pressures

By EDGAR G. HARRISON, JR., M.D., GRACE M. ROTH, PH.D., AND EDGAR A. HINES, JR., M.D.

BILATERAL determinations of blood pressure are of importance in the physical diagnosis of certain pathologic conditions involving the aortic arch or its tributaries to the upper extremities. Inequalities may be found in the blood pressure in the 2 arms of some patients who have syphilitic aortitis with aneurysm,[1-3] or who have coarctation of the aorta proximal to the left subclavian artery[4, 5] or inflammatory or degenerative disease of the aorta such as "Takayusu's disease" with which the patient may be pulseless at times.[6] The pathology of acquired diseases of the aorta which may be manifested clinically has been reviewed by Edwards.[7] It also is generally accepted that differences in blood pressure in the arms may be noted in association with marked unilateral narrowing of an artery to the upper extremity,[8, 9] whether due to a congenital anomaly of the artery or an anomaly due to atheroma, embolus, thrombus, or external compression by structures in the shoulder girdle, a cervical rib, or a mediastinal tumor.

A stumbling block to attributing diagnostic significance to differences in the blood pressure in the 2 arms has been the repeated comment in the literature that disparities in bilaterally determined blood pressure have been found in a large percentage of apparently healthy individuals[2, 10, 11] and in patients[8, 12-14] without apparently unilateral pathologic changes in the arteries and that the frequency and the magnitude of these differences apparently were increased in hypertensive persons.[1, 13] Although several investigators have pointed out the importance of such inequalities of blood pressure in the diagnosis and evaluation of treatment of hypertension,[8, 12, 15, 16] other workers[17, 18] have denied emphatically that these inequalities are found in persons without asymmetric arterial abnormalities if the measurements are taken simultaneously and under basal conditions. Thus, blood pressure that is high in one arm and low or normal in the other presents the serious problem of its significance.

Roth and Kvale[19] pointed out that inequality in brachial blood pressures can result in an incorrect interpretation of results in pharmacologic tests for pheochromocytoma. In patients with permanent inequalities in basal brachial blood pressures due to structural vascular differences, a dramatic alteration in blood pressure is recorded when the basal blood pressures have been measured on one arm and then, after the administration of histamine or phentolamine (Regitine), were compared with pressures in the opposite arm. Also, if the blood pressure is not always taken in the same arm, the routine blood pressure records of such patients may indicate a pattern of paroxysmal hypertension such as is found in some patients with pheochromocytomas.

The results of studies of bilateral blood pressures in 100 or more subjects recorded in the medical literature are shown in table 1. All the investigators employed the indirect method of determining blood pressure. The inherent inaccuracies of the indirect method have been indicated by some workers as one of the reasons for the differences.[17, 18]

Since progress in medical instrumentation has made available more accurate devices such as the strain-gage manometer*[23] and Polyviso recorder† by means of which direct continu-

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*Statham Laboratories.

†Sanborn Company.

Table 1

Studies of Bilateral Indirect Blood Pressure on 100 or More Subjects

Author	Year	Subjects	Differences in blood pressure: Systolic, mm. Hg: 10 or more	Systolic, mm. Hg: 20 or more	Diastolic, mm. Hg: 10 or more	Diastolic, mm. Hg: 20 or more	Determined simultaneously
Cyriax[20]	1921	128	35%	7%	45%	4%	No
Bodenstab[21]	1925	100	Average: 11.7 mm.		Average: 9.6 mm.		No
van Balen[22]	1929	150	4%				No
Kay and Gardner[10]	1930	125	20% Usually higher on rt.	13.6%	14.4%	4.8%	No
Stieglitz and Propst[23]	1932	600	10 mm. or more systolic or 5 mm. or more diastolic in 15.7%				No
Korns and Guinand[2]	1933	1000	22.2%		21.7%		No
Southby[12]	1935	516	20 mm. or more systolic or 10 mm. or more diastolic in 60%				No
Shock and Ogden[10]	1940	102	Compared mean values (rt.-lt.): systolic = 1.6 ± 0.36 mm. diastolic = 0.36 ± 0.18 mm.				No
Amsterdam and Amsterdam[13]	1943	1000	Rt. > lt. in 70% and of these 44.6% differed by 10 mm. or more, and 12.1% by 20 mm. or more		Rt. > lt. in 65% and of these 14.3% differed by 10 mm. or more		Part of study
		272 hypertensive	Rt. > lt. in 84.4% and of these 100% differed by 10 or more; 60.5% by 20 mm. or more		Rt. > lt. in 81.9% and of these 33.3% differed 10 mm. or more; 4.2%, by 20 mm. or more		
Israel[24]	1944	125 hypertensive		18.4%			No
Heddaeus[25]	1948	100	17%		7%		Yes, combitomographs*
Rueger[8]	1951	755	50% Rt. > lt. 71.5%	13.6%	33.7%	2.4%	No
Randig, Buding and Eismann[14]	1952	100	17% > 15 mm.				No
Beckmann[11]	1953	126	31% Rt. > lt.		10.3%		Yes
Bauereisen[17]	1953	458	2.6%				Yes, optical manometer*
Hoyer[26]	1956	1600	Systolic differences of 5 mm. or more in 70% Diastolic differences of 5 mm. or more in 47% Rt. usually > lt.				No
Hagen[18]	1956	152	Compared mean values (rt.-lt.): systolic = 6.7 mm. diastolic = 0.1 mm.				Yes
Stein[27]	1956	250	16%		7%		Yes, combitomographs*

*Continuous indirect methods.

Table 2

Number, Sex and Mean Ages of 447 Patients

Method	Patients*	Total	Male	Female	Ages, yr.	S. D.
Indirect	Nonhypertensive	131	83	48	43 ± 1.1†	12.3
	Hypertensive					
	140-170 mm. Hg	127	71	56	47 ± 1.7	19.4
	170+ mm. Hg	183	107	76	51 ± 0.8	11.4
	Pheochromocytoma	6	3	3	38 ± 4.7	11.3
	All patients	447	264	183	48 ± 0.7	14.4
Direct	All patients	53	42	11	47 ± 1.7	12.4

*Excluding 3 patients who are presented separately.

†The figure after the ± is the standard error of the mean.

ous graphic measurements can be obtained, an assessment of the bilateral disparities of blood pressure was undertaken. In this study bilateral measurements of blood pressure by the 2 methods were evaluated: (1) by comparing the bilateral determinations obtained by using the simultaneous indirect and simultaneous direct (intra-arterial) methods in a group of normal subjects; (2) by comparing the results of bilateral, nonsimultaneous and simultaneous determinations obtained by the indirect method in a large group of patients; (3) by obtaining bilateral intra-arterial blood pressures on a selected group of patients who were found to have bilateral inequalities of blood pressure by the simultaneous indirect method, and (4) by determining the effect of change in body position, age, difference in arm sizes, right or left-handedness, and antihypertensive drugs on the bilateral differences.

Materials and Methods

Control Group (14 Normal Subjects)

The control group consisted of 14 healthy men whose ages averaged 23 years and ranged from 18 to 32 years. Bilateral blood pressures were determined simultaneously in both brachial arteries by the indirect method and by the intra-arterial or direct method on each subject. Direct measurements were obtained from the radial arteries in 9 subjects and from the brachial arteries in 5.

Patients Studied

The brachial blood pressures were determined bilaterally by the indirect method on 450 patients examined at the Mayo Clinic. The results in 3 of these patients will be presented separately. Of the remaining 447 patients 264 were males and 183 were females. The average age was 48 years, with a range from 15 to 83 years. The 447 patients were divided into hypertensive and nonhypertensive groups on the basis of whether the resting blood pressure was 140 mm. Hg systolic and 90 mm. Hg diastolic or more. The hypertensive group was further divided into those with systolic blood pressures of 140 to 170 mm. Hg and those with systolic blood pressures of more than 170 mm. Fifty-three patients from the entire group, predominantly those who had shown inequalities of blood pressure by the simultaneous, indirect method, were selected for bilateral, intra-arterial studies. The sex and mean ages of the patients in these groups are shown in table 2.

Indirect Method

Each subject was allowed to rest quietly in the supine position for 20 to 30 minutes. The circumference of each arm was measured in centimeters at a point 10 cm. above the medial epicondyle by means of a steel tape.

Following this, nonsimultaneous measurements of the blood pressure in the arms were taken in order to assess the inequalities that may be found by this method in routine physical examinations. Then, auscultatory blood pressure readings were taken simultaneously on the arms by 2 observers, using a bilateral cuff apparatus (fig. 1). Three determinations were made with an interval of 1 minute between observations. Since the apparatus was constructed by joining 2 Tycos aneroid sphygmomanometers with 13-cm. cuffs to a single rubber hand-bulb through a Y-connection, simultaneous inflation or deflation of the cuffs was obtained. In order to insure accuracy of registration, the aneroid sphygmomanometers were checked periodically against each other as well as against standard mercury manometers. Systolic pressures were recorded at the first sounds heard over the brachial arteries and diastolic pressures at the disappearance of the sounds. The recommendations of Bordley and associates[29] for determinations of blood pressure on human beings were followed.

Three bilateral simultaneous indirect determinations of blood pressures were made on 50 of the

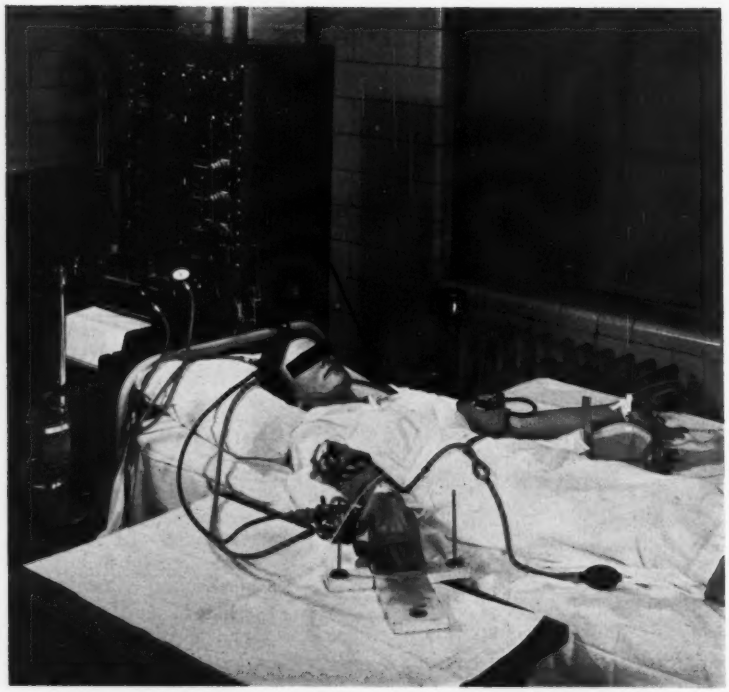

Figure 1

Apparatus arranged for bilateral direct radial and indirect brachial blood pressure determinations on a subject. The strain-gage manometers are located adjacent to the subject's wrists and are connected to the radial intra-arterial needles and to the calibration system and recorder (left). *The bilateral brachial cuff apparatus seen here was removed during the direct recordings.*

patients while they were in the supine position and later in the sitting position and on 19 hypertensive patients before and during antihypertensive drug therapy.

After the indirect readings of blood pressure the subject rested for 20 to 30 minutes before bilateral intra-arterial studies were undertaken.

Bilateral Direct Method

The apparatus employed (fig. 1) was a modification of the equipment used by Godden, Roth, and Hines[30] in a study of the changes in intra-arterial pressure during immersion of the hand in ice-cold water. Its composition was outlined by them and was based on the work of Wood, Lambert, and Burchell.[31] Through the use of the bilateral hypodermic strain-gage manometric systems, simultaneous arterial pressure pulses were inscribed by the Sanborn multichannel recorder. When brachial intra-arterial studies were made, the arms were supported on folded towels and 20-gage needles were inserted into the arteries just medial to the biceps tendons at the cubital regions after local anesthesia was obtained with 1.5 per cent procaine hydrochloride.

The calibration system consisted of an aneroid gage which was connected by rubber tubing to a rubber hand-bulb and to a bottle containing 100 ml. of sterile, heparinized saline solution. The bottle was inverted and connected to both strain gages by means of a Y-connection and rubber tubing. Through this system, simultaneous calibrations at increments of 10 mm. Hg were obtained at the beginning and end of each record. The meniscus of the saline solution and the sites of arterial punctures were leveled to the midline of the side of the chest at the third intercostal space.

The paper speed was set at 1 mm. per second and the paper was allowed to run at least 20 minutes at the beginning of a recording. Then, the speed was changed to 5 or 10 mm. per second for 3 brief intervals spaced 1 minute apart. The systolic and diastolic levels of simultaneously recorded bilateral pulse pressures were measured once for each of these intervals. More detailed pressure pulse contours were obtained at paper speeds of

Table 3

Control Group: Mean Bilateral Blood Pressures Determined by Simultaneous Indirect and Direct Methods

	Subjects	Blood pressures, mm. Hg					
		Right		Left		Differences (Rt.-Lt.)	
		Mean	S. D.	Mean	S. D.	Mean	S. D.
Bilateral systolic blood pressures							
Indirect							
Brachial	14	120 ± 1.6*	10.2	122 ± 1.4	9.1	−2 ± .6	4.0
Direct							
Radial	9	123 ± 2.6	13.4	122 ± 2.3	12.0	+.3 ± .7	3.5
Brachial	5	117 ± 2.6	10.2	117 ± 3.1	12.0	0 ± .8	3.2
Total	14	121 ± 1.9	12.4	121 ± 1.9	12.2	+.2 ± .5	3.3
Bilateral diastolic blood pressures							
Indirect							
Brachial	14	70 + 1.1	7.0	70 ± 0.9	6.3	−.3 ± .5	3.3
Direct							
Radial	9	69 ± 1.7	8.7	68 ± 1.7	9.0	+.5 ± .3	1.7
Brachial	5	63 ± 2.4	9.5	63 ± 2.4	9.3	+.1 ± .2	.9
Total	14	67 ± 1.4	9.3	66 ± 1.4	9.4	+.4 ± 1.4	.2

*The figure after the ± sign is the standard error of the mean.

25 mm. per second after the measurements were recorded at the lower speeds.

Bilateral Differences in Blood Pressure in the Control Group (14 Subjects)

Systolic Blood Pressures

The statistical mean bilateral systolic blood pressures and the (right-left) differences in the statistical means are tabulated for the control group in table 3. Bilateral simultaneous cuff pressures were taken 3 times on each of the 14 control subjects, thus giving a total of 42 bilateral measurements for the group. There was only a slight difference in the means for the indirect readings on both arms. However, bilateral differences of 5 mm. Hg or greater occurred in 9 simultaneous measurements and of 10 mm. or more in 3 measurements.

Mean systolic blood pressures by the direct method were the same for the 2 arms, and there was no significant difference in the mean values in either the 9 bilateral radial or the 5 bilateral brachial arteries studied. However, 6 of the 42 individual bilateral measurements differed by 5 mm. Hg or more, but none differed by 10 mm.

Variability of Differences

The differences recorded by each method were frequently inconstant in that they could decrease or increase in magnitude or become greater on the opposite side in the same individual during the 3 paired readings. A typical recording of bilateral intra-arterial blood pressures which shows this variability is presented in figure 2.

In order to evaluate this variation, the number of subjects who manifested inequality in bilateral systolic blood pressures of 5 mm. or greater for one bilateral measurement, which in another measurement increased or decreased by 5 mm. Hg on the same side or became equal on the two sides, or changed to the opposite side, was tabulated. From this tabulation we found that by the indirect method 5 of the 14 subjects had inequalities in the systolic blood pressures of 5 mm. Hg or greater and 4 of these varied in the 3 1-minute measurements. By the direct method, 5 subjects had differences of 5 mm. Hg or greater and the blood pressure differences in 2 of these 5 varied in 3 minutes; however, all varied at some time during their entire recording and none of the subjects who had a difference by the indirect method showed a similar difference by the direct method.

Diastolic Blood Pressures

A similar appraisal of the mean bilateral diastolic blood pressures in the control group (table 3) revealed essentially equal values

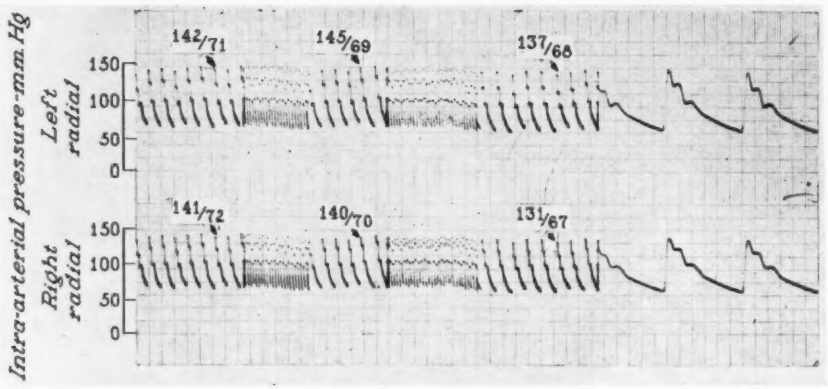

Figure 2

Direct bilateral recordings of radial pressure on a 27-year-old man of the control group showing the production of transient inequality in the systolic blood pressure. Paper speeds shown are 1, 5, and 25 mm. per second.

for the right and left sides by both the indirect and direct methods. When the incidence of bilateral differences in the indirect diastolic blood pressures were considered as they occurred in all measurements, only 5 measurements (on 3 subjects) had differences of 5 mm. or greater, and all of these were variable. None of the paired measurements differed 10 mm. or more. The direct method disclosed no differences of 5 mm. Hg or more.

Results of Studies on Patients

Bilaterally Nonsimultaneous and Bilaterally Simultaneous Indirect Determinations of Blood Pressures

Each of the 447 patients had 1 set of bilaterally nonsimultaneous measurements of the blood pressures in the 2 arms and 3 sets of bilaterally simultaneous measurements (1,341 simultaneous measurements). For the entire group by the nonsimultaneous indirect method the mean right systolic pressure was 163 ± 1.9 mm. and the mean left systolic pressure was 165 ± 1.9 mm. The mean (right-left) difference was −2.3 ± 0.6. By the simultaneous indirect method, however, the mean right systolic pressure was 168 ± 1.0 mm., the mean left pressure was 167 ± 0.9 mm., and the mean right-left difference was +0.5 ± 0.1 mm.

The same tendency also was noted in the 131 nonhypertensive and 310 hypertensive patients in that the mean bilateral values were slightly higher on the left when obtained by the nonsimultaneous method and essentially equal when obtained simultaneously. This tendency was reversed in the 6 patients who had pheochromocytomas in that the mean systolic values obtained nonsimultaneously were nearly equal and they were slightly higher on the right by the simultaneous method.

Comparison of the mean bilateral diastolic blood pressures obtained by the nonsimultaneous and the simultaneous indirect method shows near equality in each of the groups considered. The mean differences were −0.8 ± 0.4 mm. by the nonsimultaneous indirect and −1.3 ± 0.2 mm. by the simultaneous indirect method for all patients (table 4).

Bilateral Simultaneous Indirect and Direct Blood Pressures of 53 Selected Patients

The mean values of bilateral systolic blood pressure by the indirect and the direct measurements on 53 selected patients are presented in table 5. There were no marked bilateral differences by either method. No attempt was made to compare absolute values for systolic or diastolic blood pressures by the indirect and direct methods because of the lapse of time between the applications of the 2 methods.

Table 4

Selected Group: Mean Bilateral Blood Pressures by Nonsimultaneous and Simultaneous Indirect Methods

Patients	Subjects	Nonsimultaneous, mm. Hg: Right Mean*	Right S.D.	Left Mean*	Left S.D.	Difference (Rt.-Lt.) Mean*	Difference (Rt.-Lt.) S.D.	Simultaneous, mm. Hg: Right Mean*	Right S.D.	Left Mean*	Left S.D.	Difference (Rt.-Lt.) Mean*	Difference (Rt.-Lt.) S.D.
Bilateral systolic blood pressures													
Nonhypertensive	131	130 ± 1.4	15.6	131 ± 1.5	17.0	−1.4 ± 0.7	7.5	130 ± 0.7	13.6	130 ± 0.7	13.2	+0.4 ± 0.7	13.1
Hypertensive													
140-170 mm. Hg	127	156 ± 1.7	19.5	159 ± 1.5	17.3	−2.3 ± 1.0	10.8	159 ± 0.5	10.0	158 ± 0.5	10.2	+0.5 ± 0.2	3.9
170+ mm. Hg	183	192 ± 3.1	42.4	194 ± 3.0	40.6	−2.3 ± 0.1	14.5	201 ± 1.0	24.5	200 ± 1.0	23.7	+0.6 ± 0.7	16.5
All	310	177 ± 1.3	39.1	180 ± 1.2	37.5	−2.3 ± 0.4	13.1	183 ± 1.0	28.7	183 ± 0.9	28.3	+0.6 ± 0.2	4.7
Pheochromocytoma	6	168 ± 8.6	20.7	168 ± 9.7	23.2	0 ± 3.0	7.3	157 ± 4.6	19.2	155 ± 4.5	18.7	+1.9 ± 0.9	3.7
All patients	447	163 ± 1.9	40.1	165 ± 1.9	39.4	−2.3 ± 0.6	11.7	168 ± 1.0	34.8	167 ± 0.9	34.5	+0.5 ± 0.1	4.6
Bilateral diastolic blood pressures													
Nonhypertensive	131	81 ± 0.6	6.6	81 ± 0.9	10.6	0	0.2	78 ± 0.4	8.4	79 ± 0.4	8.3	−0.9 ± 0.2	4.1
Hypertensive													
140-170 mm. Hg	127	95 ± 1.0	11.3	97 ± 1.2	14.1	−1.4 ± 0.6	6.4	94 ± 0.5	9.3	95 ± 0.5	10.0	−1.4 ± 0.3	6.6
170+ mm. Hg	183	116 ± 1.9	26.9	117 ± 2.0	27.5	−0.8 ± 0.6	8.5	114 ± 0.7	16.6	115 ± 0.7	17.3	−1.4 ± 0.2	5.2
All	310	108 ± 0.8	24.2	109 ± 0.8	25.0	−1.0 ± 0.3	7.7	106 ± 0.6	17.2	107 ± 0.6	17.8	−1.4 ± 0.2	5.7
Pheochromocytoma	6	100 ± 6.5	15.5	103 ± 6.2	14.8	−2.3 ± 3.2	7.7	95 ± 2.5	10.4	98 ± 2.5	10.5	−2.9 ± 1.2	5.1
All patients	447	100 ± 1.3	26.8	100 ± 1.2	25.1	−0.8 ± 0.4	7.3	98 ± 0.5	19.5	99 ± 0.6	20.0	−1.3 ± 0.2	5.4

*The figure after the ± sign is the standard error of the mean.

Table 5

Selected Group of Patients: Mean Bilateral Blood Pressures Determined by Simultaneous Indirect and Direct Methods

Patients	Subjects	Indirect, mm. Hg: Right Mean*	Right S.D.	Left Mean*	Left S.D.	Difference (Rt.-Lt.) Mean*	Difference (Rt.-Lt.) S.D.	Direct, mm. Hg: Right Mean*	Right S.D.	Left Mean*	Left S.D.	Difference (Rt.-Lt.) Mean*	Difference (Rt.-Lt.) S.D.
Bilateral systolic blood pressures													
Nonhypertensive	11	130 ± 3.3	18.9	127 ± 1.2	6.7	+3.0 ± 0.7	4.0	126 ± 2.5	14.1	125 ± 2.8	15.9	+1.6 ± 0.8	4.8
Hypertensive													
140-170 mm. Hg	12	159 ± 1.7	10.2	159 ± 1.6	9.7	+0.1 ± 0.6	3.7	169 ± 2.5	14.8	169 ± 2.8	17.0	−0.8 ± 0.7	4.1
170+ mm. Hg	30	198 ± 2.6	24.7	197 ± 2.5	23.8	+1.0 ± 0.7	6.5	202 ± 2.6	24.5	203 ± 2.6	24.7	−1.0 ± 0.6	5.2
All	42	187 ± 2.5	27.8	186 ± 2.4	27.0	+0.7 ± 0.5	5.8	192 ± 2.4	26.6	193 ± 2.4	27.3	−0.8 ± 0.4	4.9
All patients	53	175 ± 2.8	35.0	174 ± 2.8	35.1	+1.2 ± 0.4	5.6	179 ± 2.9	36.3	179 ± 3.0	37.6	−0.3 ± 0.4	5.0
Bilateral diastolic blood pressures													
Nonhypertensive	11	75 ± 1.2	6.6	74 ± 1.3	7.2	+0.7 ± 0.7	4.1	67 ± 1.3	7.4	66 ± 1.2	6.8	+0.9 ± 0.3	1.7
Hypertensive													
140-170 mm. Hg	12	94 ± 1.1	6.8	94 ± 1.2	7.1	+0.2 + 0.8	4.6	84 ± 1.7	9.9	85 ± 1.7	10.0	−0.3 ± 0.2	1.1
170+ mm. Hg	30	114 ± 1.8	17.2	114 ± 1.7	16.1	−0.9 ± 0.6	6.0	102 ± 1.5	14.5	101 ± 1.5	14.3	+0.5 ± 0.3	2.4
All	42	108 ± 1.5	17.3	109 ± 1.5	16.8	−0.6 ± 0.5	5.7	97 ± 1.4	15.5	97 ± 1.4	15.2	+0.3 ± 0.2	2.0
All patients	53	101 ± 1.6	20.6	102 ± 1.6	20.7	−0.3 ± 0.4	5.4	91 ± 1.5	18.6	90 ± 1.5	18.5	+0.4 ± 0.2	2.0

*The figure after the ± sign is the standard error of the mean.

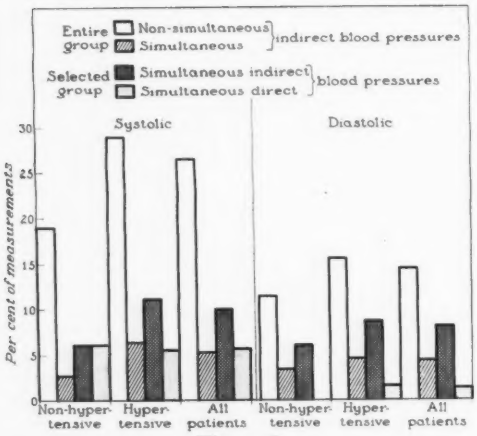

Figure 3

A summary of bilateral differences in blood pressure of 10 mm. Hg or greater obtained by nonsimultaneous and simultaneous indirect methods on 447 patients and by simultaneous indirect and simultaneous direct methods on 53 selected patients.

Incidence and Variability of Bilateral Differences in Blood Pressures

Comparison of the bilateral systolic blood pressures obtained by the nonsimultaneous and simultaneous indirect methods (fig. 3) disclosed that 26.6 per cent of the nonsimultaneous measurements in the 2 arms differed by 10 mm. Hg or greater and 7.2 per cent differed by 20 mm. or greater, whereas 5.3 per cent of the total bilateral measurements by the simultaneous indirect method differed by 10 mm. and only 0.1 per cent differed by 20 mm.

Also, small systolic differences in the bilaterally simultaneous indirect measurements, that is, differences of 4 to 9 mm., occurred with approximately equal frequency (38 to 40 per cent of measurements) in nonhypertensive as well as in the 2 hypertensive groups. Differences of 10 mm. or more occurred with approximately equal frequency in the nonhypertensive patients and in the subjects with systolic blood pressures of 140 to 170 mm. (2.8 and 2.6 per cent respectively). Of the measurements on hypertensive subjects with basal systolic blood pressures of more than 170 mm. Hg, 8.8 per cent differed by 10 mm. or greater; this indicated a slight trend toward larger differences at high levels of systolic blood pressure.

The incidence of differences in bilaterally simultaneous systolic blood pressures measured by the indirect and direct methods in 53 patients is shown in figure 4. Fifty (31 per cent) of the 159 measurements by the indirect method (3 paired measurements on each of 53 subjects) and 46 (29 per cent) of the measurements by the direct method differed by at least 5 mm. in the 2 arms. Sixteen (10 per cent) of measurements by the indirect method and 9 (6 per cent) by the direct method differed by 10 mm. or more. Both the indirect and the direct measurements tended to differ by 10 mm. Hg or more slightly oftener in hypertensive patients who had basal systolic pressures of more than 170 mm. Hg.

Thus, of the 447 patients studied by the simultaneous indirect method, 224 (50 per cent) had bilateral differences in systolic blood pressure of 5 mm. or greater and 160 (71 per cent) of these differences varied during the 3 readings. Fifty-five of the 447 patients (12 per cent) had differences of 10 mm. or more, and 30 (55 per cent) of these 55 patients had differences which varied in 3 measurements. A similar appraisal for the nonhypertensive, hypertensive, and pheochromocytoma subgroups is shown in table 6. In the selected patients the indirect method yielded bilateral differences in the systolic blood pressure in more nonhypertensive and hypertensive patients than the direct method did, and it gave differences that were more variable. Only 1 of 53 patients in the selected group had a consistent difference by both methods and this was less than 10 mm. Hg.

Of 447 bilaterally nonsimultaneous measurements of diastolic pressure by the indirect method (fig. 3), 15 per cent differed by 10 mm. or more, whereas of the 134 bilaterally simultaneous measurements by the indirect method 4 per cent differed by 10 mm. or more. The incidence of bilateral differences in diastolic blood pressures determined nonsimultaneously was greater in both the nonhypertensive and hypertensive groups. The frequency of differences of 10 mm. or more was slightly greater

Table 6

Incidence and Variability of Bilateral Blood Pressure Differences by Indirect and Direct Methods

Patients			Simultaneous indirect: Entire group: Differences,* mm. Hg 5+	10+	Simultaneous indirect: Selected group: Patients	Differences,* mm. Hg 5+	10+	Simultaneous direct: Selected group: Patients	Differences,* mm. Hg 5+	10+
Systolic										
Nonhypertensive	131	Number	67	10	11	8	2	11	5	2
		Variable	50	8		6	1		—	—
Hypertensive	310	Number	155	44	42	24	7	42	16	3
		Variable	108	21		13	3		4	—
Pheochromocytoma	6	Number	2	1	0	—	—	0	—	—
		Variable	2	1		—	—		—	—
All	447	Number	224	55	53	32	9	53	21	5
		Variable	160	30		19	4		4	—
Diastolic										
Nonhypertensive	131	Number	55	10	11	5	1	11	1	—
		Variable	34	6		3	—		1	—
Hypertensive	310	Number	138	31	42	22	6	42	2	1
		Variable	89	17		15	3		1	—
Pheochromocytoma	6	Number	4	1	0	—	—	0	—	—
		Variable	4	1		—	—		—	—
All	447	Number	197	42	53	27	7	53	3	1
		Variable	127	24		18	3		2	—

*5+ = 5 mm. Hg or greater; 10+ = 10 mm. Hg or greater.

in hypertensive than in nonhypertensive patients.

The incidences of differences in diastolic blood pressures obtained simultaneously in the 2 arms of 53 patients by the indirect and direct methods are compared in figure 4. Of 159 bilateral measurements by the indirect method, 44 (28 per cent) differed by at least 5 mm., and 13 (8 per cent) by at least 10 mm. By the direct method, 6 measurements (4 per cent) differed by at least 5 mm. and only 2 differed by 10 mm. or more. Thus, the frequency and magnitude of bilateral differences in diastolic blood pressure determined by the direct method were slightly less than those obtained by the indirect. Bilateral differences in diastolic blood pressure of 10 mm. or more were slightly more frequent among hypertensive than among nonhypertensive patients.

The bilateral differences in the diastolic blood pressure of 447 patients studied by the simultaneous indirect method varied as follows: 197 (44 per cent) had differences of at least 5 mm., and 127 (66 per cent of the 197) had variable differences in the 3 1-minute readings; 42 patients (9 per cent of 447) had differences of 10 mm. or more, and 24 patients (57 per cent of the 42) had variable differences in the 3 measurements (table 6). In the nonhypertensive and hypertensive patients in the selected group, the bilateral diastolic differences were more frequent by the simultaneous indirect method than by the simultaneous direct method, and many of these varied in the 3 measurements. None of these 53 patients had a consistent difference in the diastolic blood pressure which was revealed by both methods.

Possible Factors in the Production of Differences

Body Position

The mean values of bilateral, systolic and diastolic, indirect blood pressures of 50 patients in the supine and then in the sitting position are given in table 7. Significant bilateral differences were not seen in the mean values obtained in either position. However, 9.3 per cent of all bilateral measurements of systolic blood pressure showed inequalities of 10 mm. Hg or more when the subjects were in the sitting position compared to 3.3 per

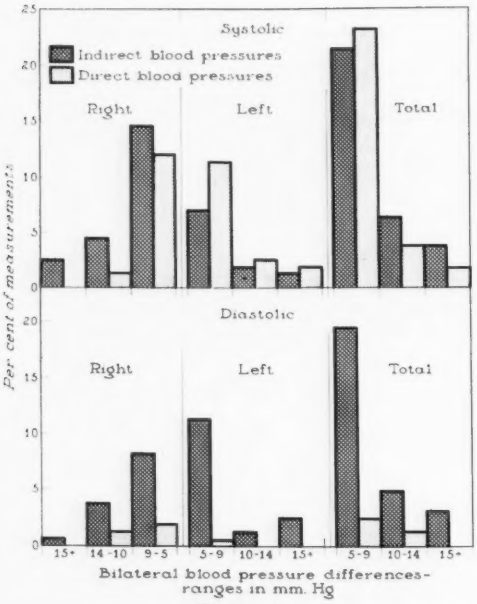

Figure 4

Bilateral differences in blood pressure found in simultaneous indirect and simultaneous direct measurements on 53 selected subjects. These are included under the side, right or left, that had the higher reading and are also totaled irrespective of side.

cent when they were supine. The corresponding diastolic differences were found in 2.6 and 1.3 per cent of the measurements respectively.

Antihypertensive Therapy and Level of Blood Pressure

The mean bilateral simultaneous indirect blood pressures of 19 hospitalized patients recorded before and during treatment with antihypertensive drugs are given in table 7. Drugs used included hydralazine (Apresoline), reserpine (Serpasil), pentolinium tartrate (Ansolysen), protoveratrine, hexamethonium chloride (Bistrium), crytenamine (Unitensin) and potassium thiocyanate. Inequalities of blood pressure due to individual drugs could not be analyzed because this was a relatively small group of patients and also because some were treated with combinations of these drugs. With the lowering of the mean values of blood pressure by antihypertensive drugs there was a shift from a slight right-sided preponderance of differences toward more equal distribution of differences on the 2 sides. Also, bilateral systolic differences of 10 mm. or more were present in 8.8 per cent of all measurements on this group before treatment and in only 3.5 per cent during treatment. Diastolic differences of this degree were present in only 1.8 per cent of measurements before treatment and 3.5 per cent of measurements during treatment. In this part of the study only 1 patient was encountered who had a static, reproducible difference, and her case, therefore, is presented separately.

Case 1

A 63-year-old housewife registered at the clinic on October 26, 1954, and was hospitalized immediately. She complained of paroxysmal nocturnal dyspnea, orthopnea, exertional dyspnea and slight swelling of the ankles of 1 month's duration. She had known that she had diabetes mellitus and hypertension for 10 years. She was aware that for a number of years her physician obtained her pulse and blood pressure more easily on the left than on the right arm.

A roentgenogram of the thorax showed marked cardiac enlargement and calcification of aorta.

Bilateral inequalities of blood pressure were reproducible in the 3 1-minute simultaneous indirect readings. The typical values obtained were right brachial artery, 170 mm. systolic and 128 mm. diastolic; left brachial artery, 254 mm. systolic and 100 mm. diastolic. A Regitine test for pheochromocytoma gave negative results when the brachial blood pressure was followed bilaterally. Bilateral direct recordings of the radial pressure were made, and they confirmed the inequality of blood pressure (fig. 5). For example, blood pressure in the right radial artery was 166 mm. systolic and 80 mm. diastolic; that in the left radial artery was 260 mm. systolic and 78 mm. diastolic. During treatment with antihypertensive drugs (including Serpasil, Apresoline, Protoveratrine and Ansolysen), 11 days after the initial study, typical bilateral indirect brachial pressures were right, 132 mm. systolic and 90 mm. diastolic; left, 180 mm. systolic and 80 mm. diastolic. The inequality was considered due to atheromatosis of the right subclavian artery, yet congenital narrowing of the right subclavian or brachial artery could not be excluded

Inequality of Size of the Arm

Ragan and Bordley[32] pointed out that in subjects with small arms blood pressure determined by the auscultatory method with a standard 13-cm. cuff tended to be too low when compared to that determined by the

Table 7

Mean Bilateral Blood Pressures Determined by the Simultaneous Indirect Method in Supine and Sitting Positions or before and during Treatment with Antihypertensive Drugs

Blood pressure	Condition	Subjects	Measurements	Right, mm. Hg Mean*	Right, mm. Hg S.D.	Left, mm. Hg Mean*	Left, mm. Hg S.D.	Differences (Rt.-Lt.), mm. Hg Mean*	Differences (Rt.-Lt.), mm. Hg S.D.
				Effect of position					
Systolic	Supine	50	150	163 ± 2.7	34.7	162 ± 2.8	35.5	+0.7 ± 1.0	12.7
	Sitting	50	150	169 ± 0.9	11.7	168 ± 0.9	11.7	+1.5 ± 0.7	8.2
Diastolic	Supine	50	150	94 ± 1.6	19.9	95 ± 1.6	20.1	−1.1 ± 0.3	3.6
	Sitting	50	150	103 ± 1.7	21.0	103 ± 1.6	20.3	−0.3 ± 0.5	6.4
				Effect of antihypertensive drugs					
Systolic	Before treatment	19	57	213 ± 4.8	35.8	210 ± 4.7	35.6	+3.2 ± 0.6	4.4
	During treatment	19	57	165 ± 3.5	26.1	165 ± 3.6	27.3	+0.2 ± 0.5	4.0
Diastolic	Before treatment	19	57	121 ± 2.8	21.0	121 ± 2.8	21.0	−0.3 ± 0.5	3.9
	During treatment	19	57	92 ± 1.8	13.6	93 ± 1.9	14.0	−0.5 ± 0.4	3.3

*The figure after the ± sign is the standard error of the mean.

Table 8

Mean Circumferences of Arms

Group and method	Subjects measured	Right, cm. Mean*	Right, cm. S.D.	Left, cm. Mean	Left, cm. S.D.	Difference (Rt.-Lt.), cm. Mean	Difference (Rt.-Lt.), cm. S.D.
Control	13	28.2 ± 0.5	1.8	28.2 ± 0.4	1.6	0 ± 0.5	1.8
Patients							
Indirect	43	28.0 ± 0.2	3.2	27.8 ± 0.2	3.3	+0.3 ± 0.1	1.3
Direct	52	28.7 ± 0.5	3.3	28.5 ± 0.5	3.4	+0.2 ± 0.1	1.0

*The figure after the ± sign is the standard error of the mean.

direct method, whereas in patients with large arms it tended to be too high. This difference was dependent on the fullness of the pulse wave. It is conceivable, therefore, that arms of unequal size could cause bilateral inequality of simultaneously determined indirect blood pressures when standard 13-cm. cuffs are used. The mean circumferences of the arms recorded are shown in table 8. The mean values on the 2 sides were essentially equal, and were about 28 cm. for both the control and patient groups.

Some subjects with a difference in circumference of the arm of as little as 4 cm. could have higher blood pressure in the larger arm or in the opposite arm or could have equal blood pressures in the 2 arms. Also, the subjects with arms of nearly equal or equal size showed inequalities of blood pressure with the higher pressure being found on either side. An interesting problem was encountered which was related to this aspect of the study. It demonstrated, as did the report of Trout and associates,[33] that blood pressure readings in extremely obese arms may be erroneous.

Case 2

The patient, a 53-year-old, obese, white woman, had mild diabetes mellitus and had been under observation at the clinic since June 1950, at which time an adenocarcinoma of the rectum had been treated surgically. Blood pressure at that time was reported to be 210/116. She was hospitalized in January 1955 because of blood pressure of 230/140. At this time her height was 60 inches and her weight 245 pounds. Her right arm measured 48 cm. and her left 50 cm. Her left arm was too large to be encircled by a Tycos blood pressure cuff, which just encompassed the right arm. Recordings of the left brachial and right radial intra-arterial pressures were made simultaneously. The

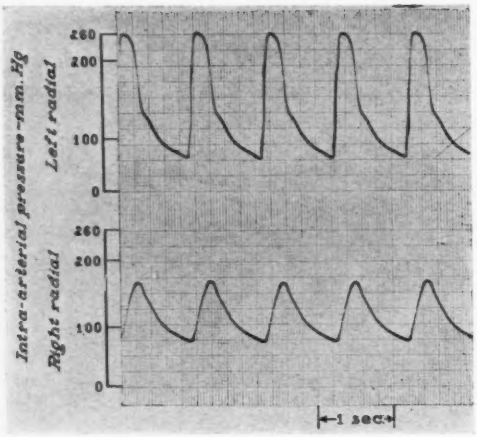

Figure 5

Bilateral direct radial pressure recordings on a 63-year-old woman who had reproducible inequality of blood pressure by both the indirect and direct methods.

cuff was allowed to remain on the right arm so that synchronous direct and indirect determinations could be compared. A portion of the tracing obtained is shown in figure 6. The right radial pressure served a double purpose in that a marked disparity in the 2 sides would be apparent at once in a bilateral tracing and it could be used to indicate that the auscultatory systolic readings were corresponding with the first pulse wave recorded on the tracing. Representative basal blood pressures were 170 mm. Hg systolic and 95 mm. diastolic in the left brachial artery by the indirect method, and 130 mm. systolic and 66 mm. diastolic in the right brachial artery by the direct method. The systolic cuff readings taken on the forearm by the palpatory method corresponded closely to the direct readings.

Right or Left-Handedness

In this study 437 patients were questioned as to whether they were right or left-handed. The 6 who were left-handed did not have blood pressures higher on the left side and the 431 who were right-handed did not have consistently higher blood pressures in the right than in the left arm or vice versa.

Age

The importance of age in relation to bilateral inequalities of the blood pressure was investigated, since loss of vascular elasticity and concomitant increase in arterial resistance to compression through arteriosclerosis might produce bilateral inequalities in the blood pressures. This study did not disclose any trend for a greater incidence of differences in blood pressure at any age level.

Arteriosclerosis

If arteriosclerosis were an important factor, one would not expect such frequently variable inequalities of blood pressures as were found. That arteriosclerosis may be a factor in certain isolated cases was brought out by the following case:

Case 3

An 83-year-old retired farmer was brought to the emergency room of a hospital in Rochester in December 1954 because of sudden transitory, sharp precordial pain, and palpitation. Marked peripheral arteriosclerosis was noted by palpation of arteries. The retinal vessels did not show hypertensive changes. The electrocardiographic findings were normal. Blood pressure recorded by the cuff method was 300 mm. systolic and 140 mm. diastolic on the right arm and 300 mm. systolic on the left arm; the diastolic pressure could not be recorded on the left arm. Korotkoff's sounds were indistinct and muffled, and several physicians had difficulty in obtaining satisfactory indirect brachial pressures. Bilateral direct determinations of radial blood pressure were done (fig. 7). Simultaneous direct readings were 130 mm. systolic and 52 mm. diastolic on the right and 92 mm. systolic and 52 mm. diastolic on the left. Bilateral application of the brachial cuff could obliterate the right radial pulse at 220 mm., yet the left radial pulse was still being recorded when the brachial cuff pressure was raised to 300 mm. Hg. The brachial arteries were palpated and found to be of "pipe-stem" firmness. A roentgenogram of the thorax was interpreted as showing calcification of the aortic arch and fibrosis of the left midlung field.

Discussion

The literature implies that the degree of discrepancies in the bilaterally determined blood pressures parallels the consistency and accuracy of the methods used to record the blood pressure. The same careful technic for determining blood pressure must be followed for each arm when bilateral blood pressures are obtained, and this technic must be applied symmetrically and simultaneously for accurate comparisons. Since indirect readings of blood pressure can be varied by the use of

a wider or a narrower cuff,[33, 34] it is obvious that a standard cuff of the same width should be used on each arm. Similarly, the instruments used must be accurate and should be checked against one another. The patient's arms must be in the same horizontal plane, for, according to Kahn,[35] blood pressure in arms placed at different levels will differ because of the hydrostatic pressure of the column of blood between the 2 points of measurement.

The data presented herein support the contention of some investigators that, if bilateral measurements of blood pressure are to be compared, strictly simultaneous bilateral measurements must be obtained. Otherwise, transient bilateral fluctuations due to vascular hyperreactivity, effects of respiration, cardiac arrhythmias, or moment-to-moment differences in pressure pulse waves may be misinterpreted as bilateral inequalities.

The subjective error of 2 observers admits a factor for possible error in the results of paired readings. Shock and associates,[36] in a careful, statistical study of 102 subjects with 48 bilateral measurements, determined that a difference in blood pressure of more than 3 mm. Hg should be measurable by 2 observers. It must be granted, however, that differences in blood pressure of less than 10 mm. are of uncertain clinical significance.

The incidence of bilateral differences in blood pressure in our series was considerably less than in many previous reports. The most prominent characteristic was their inconstancy, which also has been noted by others. Allen and Hines[15] summarized the variable nature of some differences of blood pressure in 1939: "These differences are not constant but transient and it is reasonably certain that all people have inequalities of blood pressure in the two arms at some time. Naturally, one should suspect organic disease when the differences are marked and persistent."

The height of the blood pressure is apparently related in some way to bilateral differences in blood pressure. There was a slight increase in the number and magnitude of inequalities in blood pressure of hypertensive

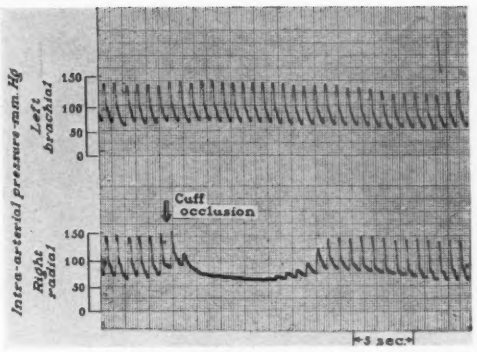

Figure 6

Bilateral, direct, *left brachial and right radial pressures in an extremely obese, 53-year-old woman. The arrow marks the beginning of dampening of the pulse wave as a right brachial cuff was inflated. This gave an indirect reading of 170 mm. Hg systolic and 95 mm. Hg diastolic.*

patients whose basal systolic blood pressures were 170 mm. Hg or more over those of hypertensive patients with blood pressures below this level or of persons without hypertension. When antihypertensive therapy had lowered the blood pressure in some patients with hypertension, the incidence of bilateral differences in systolic blood pressure also decreased slightly.

Several theories have been advanced concerning the causation of bilateral inequalities in blood pressure. Authorities generally agree concerning the existence of differences due to unilateral pathologic involvement of the subclavian or brachial arteries. Some investigators[10, 12, 13] have insisted that the differences in normal vascular anatomy are the major causative factors in all bilateral inequalities in blood pressure. Proponents of a structural explanation have defended their findings of a high incidence of right-sided inequalities by considerations of the anatomic arrangement of the aortic arch. Southby[12] proposed that since the innominate artery is closer to the source of pressure and since it is more in the direction of flow of blood from the ascending aorta, the blood pressure should be higher in the right brachial artery than in the left brachial. This, however, does not explain the existence of equality of blood

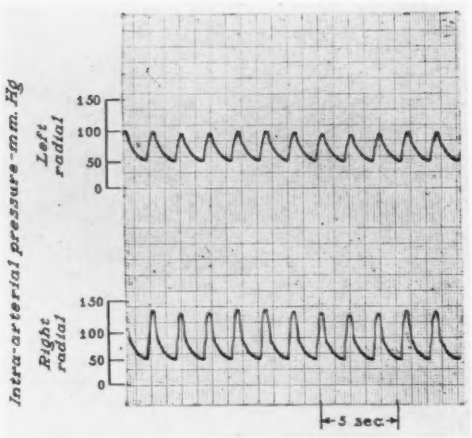

Figure 7

Bilateral, direct, radial pressures in an 83-year-old man with marked arteriosclerosis. Inflation of bilateral brachial cuffs failed to obliterate the left radial pulse waves even when the cuffs were inflated to a pressure of 300 mm. Hg. The right radial pulse was obliterated at cuff pressure of 220 mm. Hg. Note also the constant inequality of radial pressures apparently due to arterial structural differences.

pressure on the 2 sides or of left-sided elevation in some persons, nor does it explain variable differences. Also, it is difficult to project this concept beyond the sites of the orifices of the innominate and left subclavian arteries. Perhaps a comparison of catheterization pressures from these vessels will eventually disclose the importance of the normal anatomy of the aortic arch in the production of blood pressure inequalities.

Southby[12] also classified his patients according to age groups and did not find a relationship between increasing age and the magnitude of the differences in blood pressure found. Stein[27] found a tendency for greater differences with increasing age. In our study 2 older patients were encountered on whom reproducible inequalities of blood pressure were found, and it appears to us that atherosclerosis may be a major cause of differences in some patients. Randig and co-workers[14] proposed that increased rigidity of the arteries of older patients may give differences in blood pressure in 2 ways: (1) by increase in the unilateral resistance to compression, and (2) by the presence of small patent channels through which the blood can pass when the artery is compressed by the inflated cuff. In young patients they contended that differences in tonus of the arterial wall might be a major factor in differences in blood pressure.

Tissue factors were considered by Phipps,[37] in 1915, who placed a layer of fat meat about the arm beneath the cuff. This did not change the blood pressure, and he inferred that determinations of the brachial blood pressure are not affected by the thickness of the tissue surrounding the artery as much as by the position of the artery in relation to bone and muscle. Yoshino[38] noted a higher systolic blood pressure in the larger arms of athletes or laborers who used mainly 1 arm in their endeavors. Ragan and Bordley,[32] who studied blood pressure on 1 arm only, reported that dependent on the width of the cuff used, the indirect values could be too high in patients with large arms or too low in those with small arms. In our study inequality in the size of the 2 arms was not a factor in producing differences in the blood pressure. We also found, as previously pointed out in the literature, that the dominant hand is not a factor in inequality of blood pressure, since left-handed persons may have a higher pressure on the right and vice versa.

Wiggers[39] has reviewed the complex dynamic reactions induced by compression of an artery, including production of Korotkoff's sounds and augmentation of the impinging pressure pulse, as well as its loss of energy in opening up a collapsed vessel, and pointed out that the answers to such basic problems are incompletely understood and need further investigation. Similarly, the cause of transitory inequalities of blood pressure in bilateral simultaneous determinations has not been clarified as yet.

In 1953 Beckmann[11] postulated that differences in systolic blood pressure are due to changes in vascular elasticity which have both central and peripheral causes and that diastolic differences are due to differences in peripheral resistance. Bauereisen,[17] reporting

in the same year, stated that these differences do not appear in a healthy subject under stationary circulatory conditions. The differences that he found in 12 of 458 healthy students could not be reproduced by a bilateral optical sphygmographic method. He stated that when differences appear, they are expressions of regulatory processes acting through a central resistance to flow or change of vascular elasticity.

In the present study, however, clinically significant differences in blood pressure (10 mm. or greater) did occur in some subjects, and smaller differences occurred much more frequently under basal conditions. Transitory differences in pressure found by both the simultaneous indirect and direct measurements may be due to a unilateral change in arterial elasticity or vascular resistance, as postulated by previous investigators, and mediated through dynamic neurovascular controls, operating even at rest. A factor of amplification of the systolic peaks through reflected waves from unequal peripheral resistance would be of greater importance in the direct determination, since in the indirect method the peripheral circulation is occluded until the systolic level is reached. Perhaps additional factors incident to compression of the arteries by the cuffs may have accounted for the greater frequency of differences found by the simultaneous indirect method than by the direct method.

In some patients studied herein by the bilateral direct method and on whose arms we inflated and then deflated a brachial blood pressure cuff, the pulse waves subsequently recorded varied markedly from those on the opposite side. Ragan and Bordley[32] in a comparison of indirectly and directly determined blood pressures found that slow occlusion with the cuff proximal to the site of direct measurement was followed by a rise of the diastolic pressure above that in the unoccluded artery, and in addition there was a marked auscultatory gap. With fast inflation of the cuff this did not occur. They stated that prolonged partial occlusion of the veins of the arm during inflation of the blood pressure cuff affects the arterial as well as the venous pressure distal to the cuff. This suggests that study of the partial unilateral venous occlusion together with bilateral determinations of the blood pressures by the direct method might elucidate the importance of venous factors in the production of bilateral inequalities. This is but one of the facets of the problem requiring additional investigation.

In the course of our study, we found only 1 patient who had a marked and reproducible bilateral difference in blood pressure by both the simultaneous indirect and direct methods. This difference was considered to be due to asymmetrical occlusive arterial disease. The blood pressure record of such a patient may suggest paroxysmal hypertension, and pharmacologic tests for pheochromocytoma may be misinterpreted as giving positive results, if the bilateral determinations of blood pressure are made nonsimultaneously on the arms. In addition, 2 patients were encountered who had pseudohypertension, in that indirect readings of blood pressure were found to be falsely high when compared to those obtained by the direct method. One of these patients had advanced arteriosclerosis and the other was extremely obese. This suggests that bilateral simultaneous determinations of blood pressure as employed in this study are not only of value in detecting asymmetrical pathophysiology of the aortic arch or its tributaries, but also may be useful in the evaluation of certain hypertensive patients, especially those being tested for pheochromocytoma or considered for antihypertensive therapy.

Summary

Bilateral determinations of the blood pressures were made nonsimultaneously and simultaneously by the indirect method under basal conditions on 447 patients. In this group 26.6 per cent of the paired measurements by the nonsimultaneous indirect method exhibited systolic differences of 10 mm. Hg or greater and 15 per cent exhibited diastolic differences of this magnitude, whereas only 5.3 per cent of the measurements by the simultaneous indirect method had systolic differences and

only 4 per cent had diastolic differences of this degree. This indicates that bilateral determinations of blood pressure must be performed simultaneous'y on patients being examined for possible inequalities of blood pressure.

Bilateral differences in blood pressure obtained by the simultaneous indirect and simultaneous direct methods in 14 normal subjects and 53 selected patients were compared. In the normal subjects, 3 of the 42 paired indirect measurements and none of the paired direct measurements in either the radial or brachial arteries had systolic differences of 10 mm. Hg or greater, and none of the diastolic differences were of this level. In the 53 selected patients, 10 per cent of the indirect and 6 per cent of the direct measurements of systolic blood pressure differed by 10 mm. Hg or more and 8 per cent of the paired indirect measurements of diastolic blood pressure and less than 1 per cent of the paired direct measurements differed by this amount. These differences in bilateral blood pressures were characterized by their inconstancy and lack of agreement with subsequent measurements when studied by both the indirect and direct methods, which apparently separates them from those due to altered hemodynamics from pathologic conditions of the aortic arch or its tributaries.

Bilateral differences of blood pressure are of clinical importance when they are great and are reproducible by the direct as well as by the indirect methods, as illustrated by a patient encountered in this study.

In addition, 1 case of extreme obesity and 1 of advanced arteriosclerosis were reported. Both patients were found to have pseudohypertension, which was detected in this study.

A slight increase in the incidence of bilateral differences in indirect blood pressures was found in a group of patients whose blood pressures were measured while they were in the supine and then in the sitting position.

A slight increase in the incidence of bilateral differences was found at higher levels of blood pressure by comparing the blood pressures of nonhypertensive and hypertensive patients and of hypertensive patients before and during treatment with antihypertensive drugs.

Bilateral inequalities of blood pressure did not appear to be related to the age or sex of the subjects. Likewise, differences in circumferences of the arm or right or left-handedness did not appear to influence these inequalities, and there was no marked side dominance for differences found.

Bilaterally simultaneous, indirect measurements of blood pressure should be carried out on patients with hypertension who will be treated with antihypertensive drugs. Bilateral direct measurements may be used to verify the existence of inequality of blood pressures detected by the indirect method and to determine the correct pressure to be followed. This is particularly important in patients being screened for pheochromocytomas, since such differences may produce false-positive results.

Summario in Interlingua

Determinationes bilateral del tension de sanguine esseva effectuate nonsimultaneemente e simultaneemente per le methodo indirecte sub conditiones basal in 447 patientes. In iste gruppo, 26,6 pro cento del pares de mesurationes non simultanee per le methodo indirecte exhibiva differentias systolic de 10 mm de Hg o plus, e 15 pro cento exhibivo differentias diastolic de iste magnitude, durante que in le pares de mesurationes simultanee per le mesme methodo indirecte, le incidentia de tal differentias systolic esseva solmente 5, 3 pro cento, illo de tal differentias diastolic solmente 4 pro cento. Isto significa que determinationes bilateral del tension de sanguine debe esser effectuate simultaneemente in patientes sub examine pro le presentia possibile de inequalitates del tension de sanguine.

Le tensiones al duo lateres, obtenite per simultanee mesurationes indirecte e per simultanee mesurationes directe, esseva comparate pro 14 subjectos normal e 53 seligite patientes. In le subjectos normal, 3 del 42 pares de mesurationes indirecte e nulle del pares de mesurationes directe in le arterias radial o in le arterias brachial monstrava un differentia systolic de 10 mm de Hg o plus, e nulle del differentias diastolic esseva de iste ordine de magnitude. In le 53 seligite patientes, 10 pro cento del indirecte e 6 pro cento del directe mesurationes monstrava differentias systolic de 10 mm de Hg o plus, e 8 pro cento del indirecte e minus que 1 pro cento del directe mesurationes monstrava differentias diastolic de ille magnitude. Iste differentias inter le tensiones del sanguine al duo lateres esseva characterisate per inconstantia e in-

congruentia con subsequente mesurationes, tanto in le uso del directe como etiam in le uso del indirecte methodo. Iste characteristica differentia los ab illos causate per un alteration del hemodynamica in consequentia de conditiones pathologic in le arco aortic o in le tributarios de illo.

Differentias bilateral del tension de sanguine es de signification clinic quando illos es marcate e quando illos es reproducibile tanto per le directe como etiam per le indirecte methodo. Isto es illustrate per le caso de un del patientes includite in le presente studio.

Es reportate in plus un caso de extreme obesitate e un altere de arteriosclerosis avantiate. In ambe iste casos, le presente studio detegeva le facto que le patiente habeva pseudohypertension.

Un level augmento in le incidentia de differentias bilateral del indirecte tension de sanguine esseva constatate in un gruppo de patientes in qui le mesurationes esseva effectuate primo quando illes se trovava in decubito dorsal e postea quando illes se trovava in position sedente.

Un leve augmento del incidentia de differentias bilateral esseva constatate a plus alte nivellos del tension de sanguine in un comparation del mesurationes in patientes con e sin hypertension e etiam in un comparation del mesurationes in patientes hypertensive ante e post le tractamento con drogas antihypertensive.

Le inequalitates del tension de sanguine al duo lateres non pareva esser relationate con le etate o con le sexo del subjectos. Similemente, differentias in le circumferentias del bracios e dexterismo o sinistrismo non pareva influentiar iste inequalitates, e le differentias constatate non exhibiva un marcate dominantia de un latere super le altere.

Simultanee indirecte mesurationes bilateral del tension de sanguine deberea esser effectuate in patientes con hypertension qui es candidatos pro un therapia a drogas antihypertensive. Directe mesurationes bilateral pote esser usate pro verificar le existentia de inequalitates lateral del tension del sanguine detegite per le indirecte methodo e pro determinar le correcte tension como base del observationes subsequente. Isto es particularmente importante in patientes investigate pro pheochromocytomas, proque tal differentias es capace a producer resultatos falsemente positive.

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It may naturally be supposed that the erroneous view which Laennec took of the heart's action, led to corresponding errors in his doctrines of auscultation. Yet these are, fortunately, not of such magnitude as might be expected. With one exception—that of considering loudness of the second sound to be an indication of dilatation of the auricles, the errors are those of omission, and of incorrect explanation. The omissions are considerable and important. He was not aware of a fact noticed by the writer several years ago, that bellow-murmurs are produced by regurgitation through the valves.—J. Hope, M.D. *Diseases of the Heart and Great Vessels.* London, William Kidd, 1832, p. 14.

Adult Endocardial Fibroelastosis Associated with Dextrocardia and Situs Inversus

By FRANKLIN G. HOFFMAN, M.D.

ENDOCARDIAL thickening may be due to a variety of causes, among which are primary myocardial lesions, hypertension, congenital anomalies of the coronary arteries, developmental cardiac defects[1-3] beriberi heart disease,[4] progressive systemic sclerosis,[5] and idiopathic cardiac hypertrophy.[6-9] Many etiologic factors have been proposed as causative in endocardial fibrosis;[10] these include metabolic,[11] familial,[12, 13] infectious,[14] allergic causes,[15] arsenical agents,[16] and multiple factors.[17] There is lack of agreement on uniform terminology of adult endocardial fibroelastosis because of uncertainty concerning its etiology. In addition, pathologic features show significant differences. This is in marked contrast to the well-documented counterpart in infants and children. Geographic differences further add to speculation with regard to the various aspects of endocardial fibroelastosis.

Selye[18] produced subendocardial necrosis in rats after suitable conditioning with corticoids, sodium salts, and stress. Endocardial fibrosis developed in these areas; when animals were pretreated with magnesium chloride, however, endocardial fibrosis did not develop.

Endocardial fibrosis without elastosis has been observed repeatedly in cardiac lesions of patients with the malignant carcinoid syndrome.[19] These changes are restricted to the right side of the heart, specifically the pulmonary and tricuspid valves, and the right atria, except in the presence of a patent foramen ovale. In the latter instance the mitral and aortic valves may be involved. Thus, serotonin has a direct proliferative action on fibrous tissue but is destroyed by the lungs; consequently, only the right heart is exposed to high concentrations of it.

In a series of 109 unselected hearts studied at autopsy,[20] varying degrees of endocardial thickening were noted in about 60 per cent; in 5 per cent the thickening was severe. Two types were distinguished; first, the reparative type, characterized by fibrosis with little or no proliferation of elastic tissue; second, the compensatory, or mechanical, type appearing as hypertrophy of the endocardial smooth muscle and hyperplasia of endocardial elastica. The severe degrees were more closely related to cardiac dilatation and hypertrophy than other factors. Endocardial elastomyofibrosis was found more frequently in the outflow tract of the left ventricle. Mild degrees probably are unrelated to cardiac hypertrophy and dilatation.

Dextrocardia with complete situs inversus is considered by some[21] not to be an anomalous condition, since there is only reversal of the circulatory path with no interference in function. The occurrence of acquired heart disease in these individuals probably is the same as in the general population.

The following case report illustrates what is believed to be the first instance of endocardial fibroelastosis associated with dextrocardia and complete situs inversus.

Case Report

The patient, a 36-year-old Negro, was well until May 1954, when he was hospitalized in Korea because of nocturnal dyspnea and cough followed by severe shortness of breath while running uphill, and swelling of the ankles. There was one episode of blood-tinged sputum 3 months prior to his initial hospital admission in Korea. There was no history of chest pain except for brief soreness across the anterior chest.

Situs inversus had been noted in 1941 (figs. 1 and 2). Past history revealed no cyanosis and a normal childhood and adolescence. There was

From the Cardiovascular Section, Veterans Administration Hospital, Columbia, S. C.

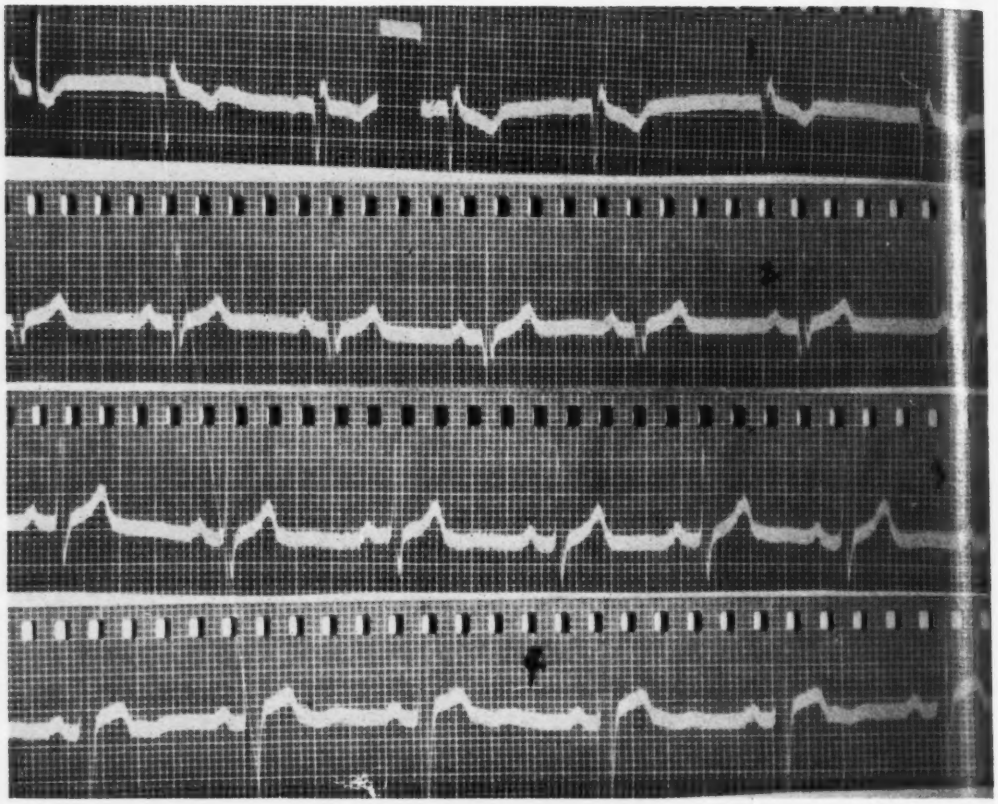

Figure 1

Conventional electrocardiogram, June 1941. CF_4 over right precordium.

no history of rheumatic fever or other serious infectious diseases.

Physical examination revealed dyspnea, orthopnea, slight cyanosis, and distended neck veins. The apical impulse was in the fifth intercostal space in the right midclavicular line. The heart sounds were of fair quality and regular at a rate of 100. There were no murmurs, but a systolic gallop was present. Rales and wheezes were heard in both lungs. There was no peripheral edema or palpable liver. The blood pressure was 118/110.

Complete blood count and routine urinalysis were within normal limits. Serology was negative. Blood urea nitrogen was 14.1 mg. per cent; total protein 5.8 Gm., albumin 3.7 Gm., globulin 2.1 Gm. Venous pressure was 23 cm. of water; arm-to-tongue test was 24.6 seconds, arm-to-lung 9.6 seconds. Electrocardiograms on admission and subsequently were consistent with dextrocardia. With reversal of the right and left arm electrodes, and with leads over the right precordium, there was a deep S through V_5 and T-wave changes in all precordial leads (fig. 3). X-ray at that time revealed dextrocardia and situs inversus; the cardiac silhouette was consistent with either pericardial fluid or generalized cardiac dilatation. Congestive changes were noted in the lung fields (fig. 4).

Following treatment with sodium restriction, diuretics, and digitalization, the heart size decreased almost to normal. The patient was then evacuated to a general hospital. During his flight back to the zone of interior he developed dyspnea and pain in the right lower chest, but no hemoptysis.

Further studies, all of which were negative, included sickle-cell preparations, smears and cultures of sputum, bone marrow, and gastric contents for acid fast bacilli, blood cultures, and 6 preparations for the LE phenomena. Biopsy of the gastrocnemius muscle, including skin and striated muscle, showed no pathologic changes. Blastomycin, coccidioidin, and histoplasmin skin

tests were negative. First-strength PPD was positive. An angiocardiogram, performed in October 1954 was interpreted as showing hypertrophy of the heart, predominantly left, with evidence of delay in emptying of the chambers of the left side of the heart; there was no evidence of stenosis of the major vessels or constriction of the outflow tracts, and no anomalies of the heart chambers were noted.

The patient remained afebrile except during an episode of pneumonitis that responded to penicillin. Right heart catheterization in October 1954 did not disclose the presence of a patent ductus or septal defect. Pressures in the right heart chambers and pulmonary artery were within normal limits.

In September 1955 the patient developed left hemiparesis, which eventually improved.

From February 1956 until his final admission in June 1959 he had recurrent episodes of congestive failure, and, following regulation of digitalis, sodium restriction, and diuretics, he improved. Several times he complained of pleuritic chest pain and hemoptysis. He also had episodes of right upper quadrant, right and left costovertebral angle discomfort. On one occasion urinalysis revealed albuminuria and hematuria; renal calculus was never proved. At no time during any of these admissions was there any significant change in the physical findings. Blood pressure was always within the normotensive range. X-ray and electrocardiogram remained essentially unchanged.

His final admission was on June 30, 1959, because of the development of right hemiparesis (fig. 5). He became progressively worse, lapsed into coma, and died on July 1, 1959.

Postmortem Examination

Pertinent gross findings were confined to the cardiovascular system. Complete situs inversus was found. The heart was dextroposed, with the apex pointing to the right. There was transposition of the great vessels; the aorta was on the right, the pulmonary artery was on the left, and the innominate veins were transposed. The aortic arch itself was somewhat short and gave rise on the right to the innominate, common carotid, and subclavian arteries. The heart weight was 700 Gm. It had the usual anatomic relationships noted in complete dextrocardia. No interatrial septal defect was noted. There was a fairly dense opacity noted over the anterior and posterior walls of the left ventricle (fig. 6). On the

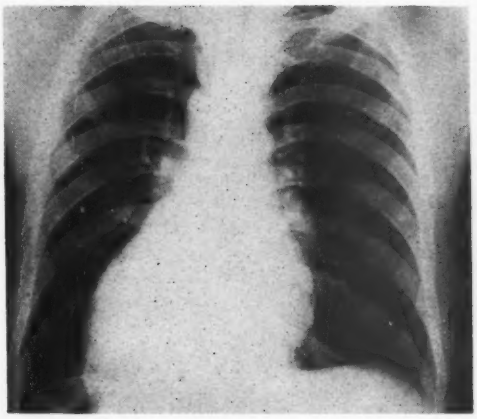

Figure 2

Routine posteroanterior roentgenogram of chest, 1950, 4 years prior to onset of congestive heart failure.

posterolateral wall of the left ventricle was a very large mural thrombus that covered an area approximately 3.0 cm. in diameter; sections through this revealed considerable fibrosis, which was also noted at the apex of the left ventricle. The valves, except for increase in circumference due to dilatation, were normal, and there were no vegetations or gross lesions. There was marked dilatation of all chambers of the heart. The left ventricle, exclusive of papillary muscle and trabeculae carneae, measured 1.0 cm. in thickness; the right ventricle measured 3.0 to 4.0 mm. in thickness. The coronary arteries, except for mirror reversal of their origins, showed no abnormalities and were soft, pliable, and patent throughout. There was endocardial thickening that extended to some extent all along the papillary muscles. There was edema and congestion of the lungs. There were small infarcts in both the right and left kidneys and the spleen. The major lesion of the brain was an old, large infarct, cortical and subcortical, in the right frontal area. No gross embolus was demonstrated on the left.

The pertinent microscopic findings were confined to the heart. Sections from the left ventricle revealed that the lining endothelium was ill defined and, in some areas, completely

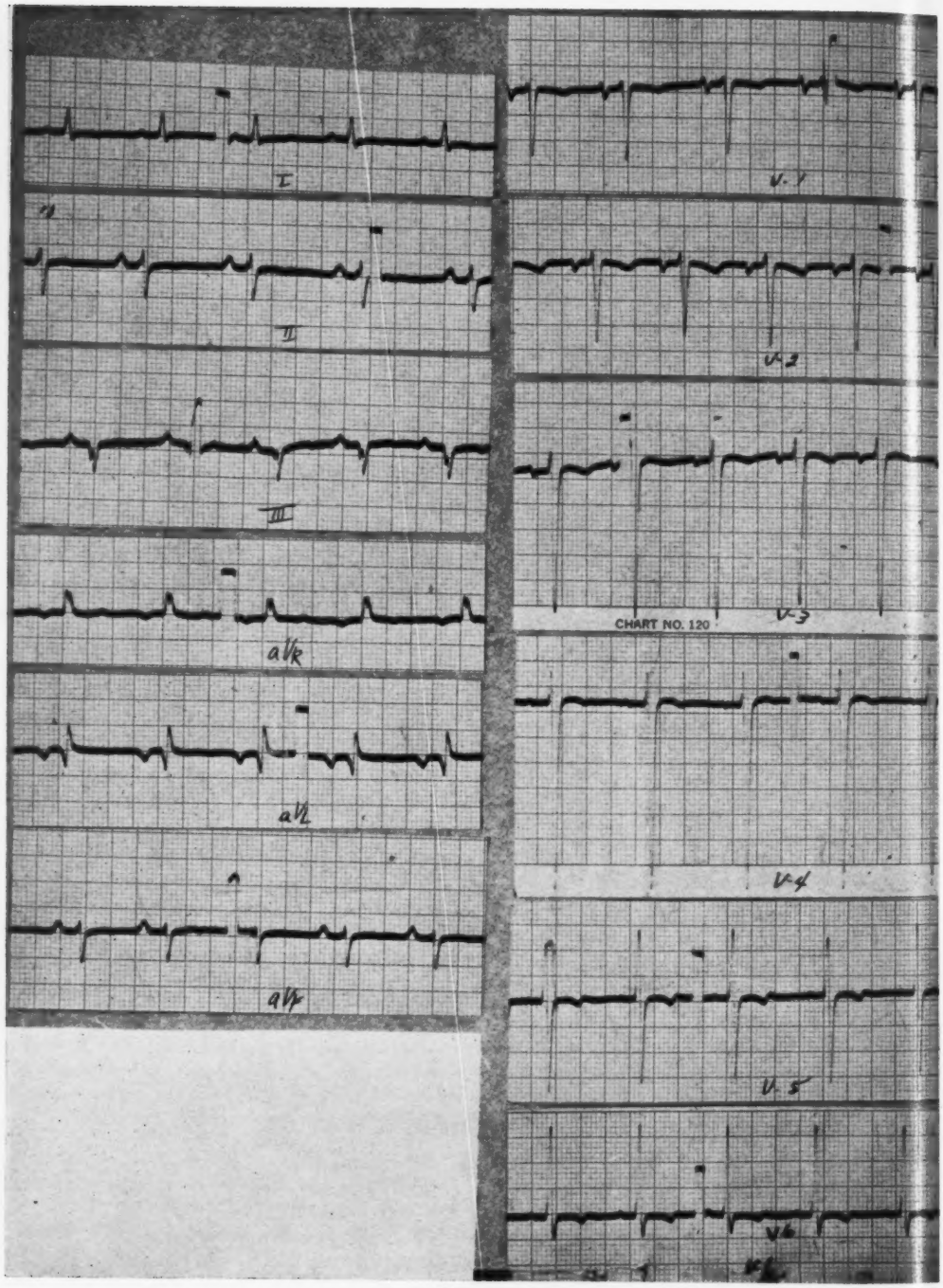

Figure 3
Electrocardiogram, May 1954, during initial admission.

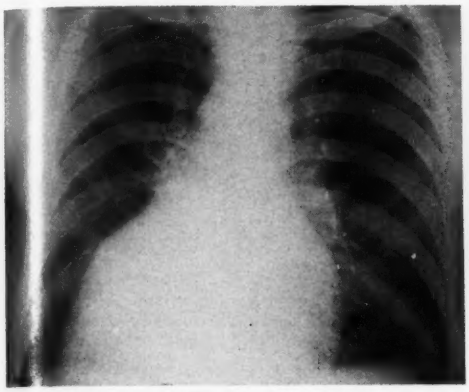

Figure 4

Posteroanterior roentgenogram of chest, May 1954, during initial admission.

absent. Beneath the endocardium there was a wide zone of dense collagenous fibrous tissue. This fibrotic area contained a few capillary channels (fig. 7). Some lymphocytic infiltration and focal areas of fibrosis were noted deeper in this fibrotic zone (fig. 8). Sections that were stained for elastic tissue revealed no absolute increase in elastic tissue; however, fragmentation of some of the elastic tissue fibers was noted (fig. 9). There was considerable hypertrophy of the cardiac muscle fibers (fig. 10). There was swelling of individual fibers, which were 2 or 3 times normal size, with variation in staining capacity and configuration of the nuclei. Microscopic evidence of infarction in the spleen and kidneys was also present, as well as a recent partial thrombotic occlusion of the left middle cerebral artery. There was destruction of the right cerebral cortex with a considerable degree of gliosis.

Discussion

Mirror-image dextrocardia for the most part is unassociated with other intracardiac anomalies. On the other hand, approximately 90 per cent of autopsied cases of dextroversion have associated developmental defects, usually of conotruncal origin.[22] An example of thickened mural endocardium in a case of corrected transposition of the great trunks was noted by Abbott.[21]

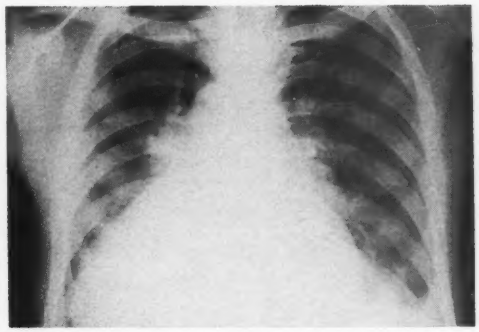

Figure 5

Posteroanterior roentgenogram of chest, May 1959, shortly before final admission.

The pathologic features of this case suggest a combination of lesions—cardiac hypertrophy on the one hand, endocardial fibroelastosis on the other. The patient's course was one of progressive deterioration punctuated by recurrent bouts of congestive failure and thromboembolic episodes. Terminally a cerebral embolus was suspected. At no time were any of the known etiologic causes of heart disease elicited, in spite of exhaustive studies. It was only shortly prior to death that the diagnosis of endocardial fibroelastosis was strongly entertained. Cardiac catheterization failed to reveal any significant features to suggest the constrictive syndrome in the absence of an elevated right ventricular end-diastolic pressure. In the infantile type of fibroelastosis, normal right heart pressures are more frequently found; this would tend to indicate, unless the right outflow tract is involved, or pulmonary obstruction is present, that significant right ventricular end-diastolic pressure changes may be absent.

The mechanism whereby endocardial fibroelastosis leads to cardiac hypertrophy still is speculative; however, it is currently accepted that a mechanical factor, i.e., the thickened, rigid endocardium, simulates constrictive pericarditis and interferes with systolic ejection. This has been borne out by hemodynamic studies.[23] Linde and Adams[24] devised an ingenious method of measuring the in vitro length tension of the endocardium

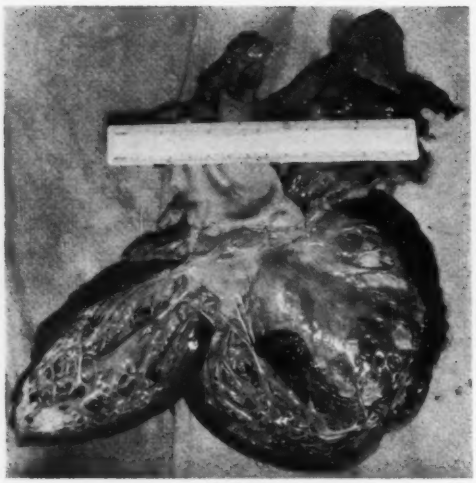

Figure 6

Left heart chambers. A portion of the septal wall is deflected to show areas of endocardial thickening. Note mural thrombus in posterior wall of left ventricle.

in patients with endocardial fibroelastosis. They compared the affected tissue with normal endocardium and were able to demonstrate greatly increased tensile strength in endocardial fibroelastosis as it resisted stretching. These studies further tend to emphasize the splinting effect of the thickened endocardium and consequent loss of ventricular contractility and resulting heart failure observed clinically.

Fundamentally, as the term implies, the changes are seen most commonly in the endocardium. In most instances there is cardiac enlargement with dilatation and hypertrophy of one or more chambers.[17, 25] The heart weight varies from 300 to 795 Gm. As a rule there are no striking changes in the atria, although, on occasion, endocardial thickening with mural thrombi has been described. The remarkable feature is the pale gray thickening of the endocardial surface, varying from 1.0 to 4.0 mm. These changes usually are characteristically distributed over the trabeculated surface of the ventricles, mostly at the apex of one or both ventricles, and tending to involve the posterior ventricular wall. It is unusual to find involvement of the ventricular septum and the subaortic or subpulmonic area. Although valvular involvement is not a constant attribute, moderate degrees of thickening are not uncommon and may produce stenosis.[26, 27] Chordae tendineae also may show thickening with fusion, shortening, and adherence to the posterior wall. Vegetations in the valves are rare, although fibrinous verrucal growths may be found. Mural thrombi are not uncommon on the ventricular wall and, on occasion, the atrioventricular valves. There may be a variable amount of focal or diffuse fibrotic change in the subjacent myocardium. The coronary arteries are patent. The pericardium is normal. A constant microscopic finding is fibrosis of the collagenous tissue, and sometimes areas of hyaline degeneration. Elastic tissue may be present, but the amount and distribution are irregular. Associated focal collections of lymphocytes, some hypertrophy of individual muscle fibers, and varying amounts of linear fibrosis may be found in the deeper layers of the myocardium. Occasionally, fibroelastic intimal hyperplasia of the smaller vessels, with subsequent narrowing of the lumina, may be found.

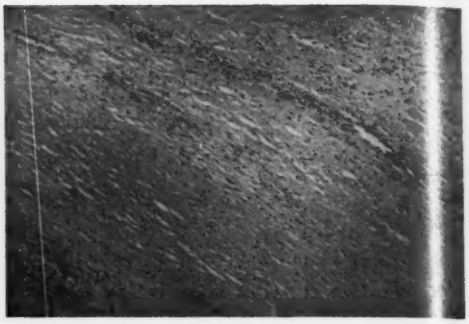

Figure 7

Left ventricular endocardium showing marked fibrosis. Hematoxylin and eosin stain.

The frequent occurrence of endocardial fibroelastosis in infants and young children has prompted many authors to consider this as evidence of congenital rather than acquired origin. This view is not easily refutable. Furthermore, similar lesions have been reported in adolescents and young adults more fre-

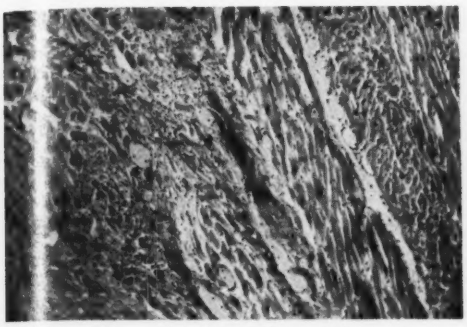

Figure 8

Left ventricular myocardium showing areas of fibrosis and cellular infiltration. Hematoxylin and eosin stain.

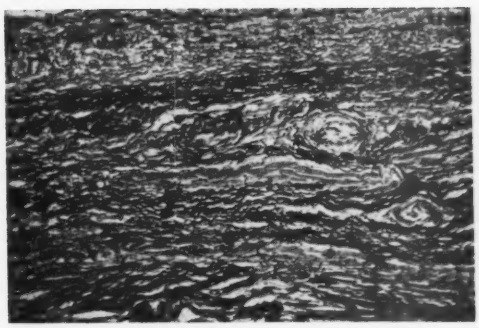

Figure 9

Endocardium and adjacent myocardium showing elastic tissue. Weigert's elastic-tissue stain.

quently than in older age groups.[28] The possibility that endocardial fibroelastosis found in the second or third decade may represent persistence of this abnormality from birth cannot be denied. In these instances the assumption appears tenable that disturbed cardiac function did not manifest itself until adolescence or early adulthood for a variety of reasons, including limited involvement of the endocardium. The association of endocardial fibroelastosis with dextrocardia with complete situs inversus by no means contradicts this reasoning in view of the rationale of Abbott.[21] Hence, this explanation for the occurrence in the later decades of life seems less tenable.

Endocardial fibrosis is most commonly seen in young adults;[29, 30] however, older age groups are not exempt.[31–33] The entity is rarely suspected during life, since in most instances, it is an unexpected autopsy finding. The clinical picture is one of progressive cardiac failure of rather insidious onset. The failure may run a rapid course of only a few weeks or may extend over a period of years. In some instances exploratory operations have been performed because of suspected constrictive pericarditis.[23, 34] Fever usually is absent. Pain is an inconstant feature and, when present, may be indistinguishable from angina. The history is devoid of any features suggesting an etiologic factor. Blood pressure usually is normal but may be elevated during periods of congestive failure. There is no general agreement that the pitch of the early diastolic sound is higher in pericardial calcification than in endocardial fibrosis.[35] There is cardiac enlargement but no characteristic silhouette or specific chamber disproportion. Electrocardiograms may show nonspecific changes ranging from T-wave abnormalities to QRS distortion, and, on occasion, atrioventricular block of varying degree. Recently complete heart block with Stokes-Adams attacks has been observed.[33, 37] As a rule, arrhythmias and conduction disturbances occur sometime during the clinical course; these usually are difficult to manage.[38] Striking eosinophilia has been reported in some cases.[27, 39, 40]

Ancillary studies sometimes are helpful but by no means pathognomonic. Cardiac catheterization studies reveal restricted ventricular contraction and filling, and impaired ejection of blood.[23] Similar hemodynamic studies have been found in other entities that constitute the constrictive syndrome, such as constrictive pericarditis,[41] diffuse myocardial fibrosis,[42, 43] cardiac amyloidosis,[44] and in cases of pectus excavatum.[45] These findings have been adequately summarized by other authors.[38, 42] There are no constant symptoms, signs, or auxiliary features that unequivocally aid in making the diagnosis of endocardial fibroelastosis in the adult. Recent biplane angiocardiographic studies in children[46] demonstrate the "unchanging size and contour of the left ventricle," a sign considered to be of value in the interim or interval diagnosis of congenital

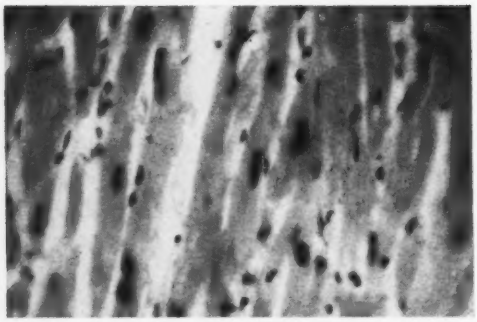

Figure 10

Myocardium showing hypertrophy of cardiac muscle fibers and variations in nuclear staining and configuration. Hematoxylin and eosin stain.

endocardial fibroelastosis. Similar studies in adults, and in the case herein presented, have been of little aid and only reflect delayed intracardiac circulation or eliminate other associated lesions.[38] The diagnosis usually is one of exclusion. One of the chief features in differential diagnosis is the frequently associated thromboembolic episode in endocardial fibroelastosis. The real difficulty may arise when constrictive pericarditis is associated with cardiomegaly. Although this entity is being more frequently recognized, it still is uncommon and is of more than academic import, since decision to operate may rest on the evaluation. It is obvious that one does not wish to neglect the surgically curable lesions, such as constrictive pericarditis.

It would appear, from a critical review of the literature, that endocardial fibrosis is one of a group of entities that has been included in a wide spectrum of seemingly related conditions. Several variants have been reported from different areas of Africa. Higginson, Gillanders, and Murray[47] have described a common type of endocardial fibrosis in the Bantu, characterized by cardiac enlargement, interstitial fibrosis, and cardiac muscle hypertrophy. These authors are of the opinion that nutritional deficiency, not necessarily thiamine, plays a distinctive role in etiology. In East Africa, Davies and others[48–50] noted that endocardial fibrosis was responsible for about 14 per cent of cardiac deaths. Extensive fibrosis of the endocardium and subjacent ventricular myocardium, commonly involving the atrioventricular valves, was noted at autopsy. Becker and his group[51] reported a series of 40 patients (32 Bantu, 8 Europeans) and presented evidence to suggest that these lesions are due to collagen degeneration and its associated ground and cement substances in the endocardial connective tissue. None of the lesions showed characteristics compatible with known collagen disease.

In the United States the well-known series of endocardial fibroelastosis reported by Thomas et al.[52] has been noted. They believed that the lesions described in their series differed quantitatively from those reported by Davies and his group. Another group of cases, originally described by Löffler,[53] resembled constrictive pericarditis but showed extensive endocardial fibrosis with marked eosinophilia.[40] Similar cases have been reported recently in this country.[27, 39] Isolated instances of endocardial fibrosis with extensive myocardial fibrosis have been noted; in these cases the endocardial lesions are not so prominent as those in the myocardium.[14, 54, 55] To add to the confusion, cases of cardiac enlargement of unknown etiology, in which marked hypertrophy of individual cardiac muscle fibers and minimal endocardial changes are noted, have been included in cases of endocardial fibrosis.[56–58] Hemodynamic studies in these cases have revealed no evidence to suggest that the findings are representative of the constrictive syndrome. Whether this entity is part of the spectrum of endocardial fibrosis cannot be disputed at this time.

Summary

The clinical and pathologic features of the first case of endocardial fibroelastosis in an adult, associated with dextrocardia and situs inversus, is reported. Difficulties in diagnosis are evident. It is considered that the occurrence of this lesion in this patient is not evidence of a congenital origin. Other intracardiac defects are rarely found associated with dextrocardia and situs inversus. The incidence of acquired heart disease in this group prob-

ably is no different from that in the general population.

Endocardial fibroelastosis and its closely related entities in the adult may pose a difficult problem in differential diagnosis. The implications involved are realistic, since exploratory thoracotomy may be considered if constrictive pericarditis cannot be ruled out. This entity should be suspected in patients, particularly young adults, with progressive congestive failure where the etiology is obscure. Patients over 60 years of age with Stokes-Adams disease, in the absence of unequivocal evidence of arteriosclerotic heart disease or aortic stenosis, should also be suspected of having this entity.[33, 37] The frequent occurrence of thromboembolic episodes is more often associated with endocardial fibroelastosis than with other entities. Efforts to arrive at a definite diagnosis should be made, and exploration advised when constrictive pericarditis cannot be ruled out. Unfortunately, cases of endocardial fibrosis, myocardial fibrosis, and probably similar entities comprising the constrictive syndrome, on occasion will be found at operation.[59] This difficulty may arise if constrictive pericarditis is associated with cardiomegaly.

Acknowledgment

The author wishes to thank Dr. S. L. Zimmerman, Chief of Medical Service, for helpful criticism, and Dr. John D. Reese, Chief of Pathology Service, for aid in preparation of the pathologic material.

Summario in Interlingua

Es reportate le aspectos clinic e pathologic del prime caso de fibroelastosis endocardial, occurrente in un adulto in association con dextrocardia e sito inverse. Le difficultates del diagnose es evidente. Es opinate que le presentia de fibroelastosis endocardial in iste patiente non indica su origine congenite. Altere defectos intracardiac se trova rarmente in association con dextrocardia e sito inverse. Le incidentia de acquirite morbo cardiac in iste gruppo de patientes es probabilemente le mesme como in le population general.

Fibroelastosis endocardial e le entitates intimemente affin con illo, quando occurrente in adultos, pone frequentemente difficile problemas ab le puncto de vista del diagnose differential. Le signification de iste facto non es purmente theoric, proque un thoracotomia exploratori pote esser prendite sub consideration si pericarditis constrictive non pote esser excludite. Le presentia de iste entitate deberea esser suspicite in patientes—particularmente juvene adultos—qui manifesta un progressive disfallimento congestive a etiologia obscur. Patientes de plus que 60 annos de etate con morbo de Stokes-Adam debe etiam esser considerate como possibile candidatos pro iste diagnose si signos inequivoc de morbo cardiac arteriosclerotic o de stenosis aortic es absente. Le frequente occurrentia de episodios thromboembolic es associate plus sovente con fibroelastosis endocardial que con altere entitates. Effortios a establir un definite diagnose deberea esser facite, e un exploration deberea esser recommendate quando pericarditis constrictive no pote esser excludite. Infelicemente, casos de fibrosis endocardial, de fibrosis myocardial, e probabilemente de simile entitates pertinente al syndrome constrictive es discoperite a vices durante le intervention chirurgic. Iste difficultate pote sublevar se quando pericarditis constrictive es associate con cardiomegalia.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Libman-Sacks Syndrome. Emanuel Libman (1872-1946) Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, and Benjamin Sacks (1896-?) his then associate reported "A Hitherto Undescribed Form of Valvular and Mural Endocarditis" (read in abstract before the Association of American Physicians, Atlantic City, New Jersey, May 1, 1923 and appearing in the *Transaction of the Association of American Physicians* **38**: 46-61, Philadelphia, 1923, same title), in the *Archives of Internal Medicine* **33**: 701-737 (June) 1924.

"We have had the opportunity of studying the clinical and pathologic findings in four cases of a hitherto undescribed form of endocarditis, which we have for the present described as an atypical form of verrucous endocarditis. . . . The disease . . . ran a subacute course with fever and progressive anemia. Briefly enumerated, the clinical findings were pericarditis, white-centered petechiae, arthritis, erythematous purpuric rashes, ulcerative lesions of the mucous membranes, pleuropulmonary symptoms, embolic phenomena, enlargement of the liver and spleen, acute glomerulonephritis, a tendency to leukopenia and repeatedly negative blood cultures. Two of the patients had an eruption on the face which resembled acute lupus erythematosus disseminatus. . . ."

SYMPOSIUM ON CORONARY HEART DISEASE

Auscultatory Findings in Myocardial Infarction

By J. Scott Butterworth, M.D., and Edmund H. Reppert, Jr., M.D.

On the subject of auscultation in acute myocardial infarction James B. Herrick[1] wrote in 1912 "The heart tones have been feeble—in fact, often startlingly feeble. Feeble contraction of the weakened, anemic heart muscle accounts for the weak pulse and the weak tones." A review of current texts on heart disease[2–4] gives much the same information. Little investigative work has been done on this subject, which is not particularly surprising when one realizes that electrocardiography and not auscultation is the more precise method of diagnosis in acute myocardial infarction.

Other reasons for the lack of precise knowledge are the technical difficulties of making phonocardiograms or tape recordings and in doing hemodynamic studies during the acute phase of myocardial infarction. These difficulties include the critical condition of the patient, environmental noise, and the lack of any standardization technic for phonocardiography that allows accurate comparison of intensity and frequency of the heart sounds from patient to patient.

Bean[5] noted that the heart sounds were described as weak, distant, or muffled in about 80 per cent of 160 cases of acute myocardial infarction and the loudness of the sounds was inversely related to the degree of shock in most cases. A phonographic study of heart sounds in acute myocardial infarction was done by Parsonnet and Hyman[6] in 1931, but because of lack of accurate recording equipment at that time it is difficult to evaluate their results in light of present technics. In 1942 Masters and Friedman,[7] using better equipment, recorded phonocardiograms in 100 normal people for controls and then a series of patients with acute myocardial infarction. They reported that the first heart sound was absolutely diminished in amplitude in 24 per cent of the cases of infarction and was relatively reduced in relation to the second heart sound in 54 per cent. They also noted that an atrial or fourth sound was recorded in 83 per cent of cases with infarction but in only 38 per cent of the controls and was practically always associated with cardiac failure. Likewise, a third heart sound was present in 47 per cent of cases with infarction, but only in 12 per cent of the controls and was invariably associated with cardiac failure. Another observation was that shock was much less common in those cases with an unimpaired first heart sound.

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Normal Intensity of Heart Sounds

Many factors affect the intensity of the first and second heart sounds.[8] The sounds are accentuated when the heart is close to the precordium as in children and thin adults, and, conversely, they are diminished in obese individuals and in emphysema because of the distance of the heart from the precordium and the poor conductive qualities of fat and lung tissue.

It should be pointed out that because of the wide variation in intensity of heart sounds normally, it is extremely difficult to evaluate changes unless each individual *acts as his own control* by having phonocardiograms or tape recordings made *before* the occurrence of a disease process. Even the change from a sitting or reclining position to a supine position frequently alters the intensity of the heart sounds rather markedly and is

only one of several factors that must be controlled. Also, as far as we are aware, no one has carefully studied the intensity of the heart sounds in normal individuals confined to bed for a prolonged period of time.

Our knowledge of the changing intensity of heart sounds due to pathologic processes is fragmentary, since adequate hemodynamic studies have not been done under acute conditions. It would seem, however, that the intensity of the first heart sound (which results from the vibrations of the blood initiated by the closure of the mitral and tricuspid valves) must be related to diastolic filling and ventricular ejection time.

Since we have so little data on this subject, we can only rely on clinical observations that have shown that the heart sounds tend to be diminished in such conditions as shock, pericardial effusions, cardiac decompensation, and terminal states. Thus, when myocardial infarction is accompanied by some degree of shock, the heart sounds commonly seem to be diminished in intensity. On the other hand, we have examined many cases of acute myocardial infarction without shock and we have not been impressed with any marked changes in the intensity or character of the heart sounds. But to confuse the issue further we must confess that we have occasionally, in cases of acute myocardial infarction, noted changes in the intensity of the heart sounds from time to time in the same patient even though no objective signs (changes in blood pressure, heart rate, etc.) have occurred to indicate a change in clinical status.

Additional Sounds

When the left ventricle is dilated as the result of myocardial disease of either acute or chronic nature, a gallop sound is frequently present, which is generally accepted to be an accentuation of a normal third heart sound or a normal atrial sound. Thus, a gallop may be protodiastolic if due to accentuation of the third sound or presystolic if due to accentuation of the atrial sound. At times, both may be present as separate sounds or may be fused into a single loud diastolic sound.

Other Auscultatory Findings

Most of the abnormal auscultatory findings in acute myocardial infarction and chronic arteriosclerotic heart disease are the result of complications. These findings are often of definite diagnostic aid, since they may give information that is not readily obtainable from such tests as the electrocardiogram.

Pericarditis

While figures vary widely, about 20 per cent of cases of acute myocardial infarction are said to show pericardial friction rubs at some time.[9] This figure might be higher if continuous recordings were to be made, since some pericardial involvement has been noted in as many as 80 per cent of autopsied cases of myocardial infarction.[10] It is difficult, however, to know how much involvement is necessary to produce rubs; moreover autopsied cases are a small percentage of the total number of cases of myocardial infarction.

The pericardial friction rubs resulting from myocardial infarction have no characteristics that differentiate them from other types of pericarditis producing rubs. Rubs are probably most commonly heard 2 to 4 days following the infarction.

Perforation of the Interventricular Septum

This is an uncommon situation probably occurring in only 1 to 2 per cent of deaths from myocardial infarction[11] but the diagnosis is relatively simple. The sudden occurrence of a loud systolic murmur, usually maximal in the fourth left intercostal space with or without a thrill is sufficient evidence. Loud pericardial rubs, however, may at times be confusing. The patient usually develops increasing venous pressure and left ventricular failure and the course is generally rapidly deteriorating although a few cases have been known to survive for several months or even years.[12]

Ruptured Papillary Muscle

This may also be confused with perforation of the interventricular septum but the murmurs tend to be more bizarre, sometimes have been reported to be diastolic in time and are

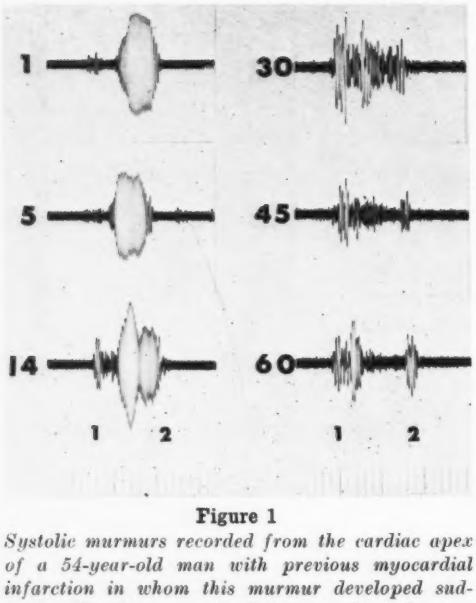

Figure 1

Systolic murmurs recorded from the cardiac apex of a 54-year-old man with previous myocardial infarction in whom this murmur developed suddenly. The figures at the left of each stethogram indicate the number of days following the onset of the murmur at which the recordings were made. Note the high-frequency musical characteristics of the murmur at the time of the first 3 recordings. The heart sounds can scarcely be identified because the murmur was so loud (grade VI) that the recording volume had to be markedly reduced. In time the murmur decreased in intensity and lost its musical character and in the last 3 recordings the heart sounds can be identified. Time intervals are 0.04 second.

usually better heard at the apex. A thrill is generally absent[13] in distinction to its rather common occurrence in interventricular septal rupture.

Figure 1 illustrates the bizarre and changing murmur encountered in a 54-year-old man who had had a previous myocardial infarction. He was awakened from sleep, and although he noted no precordial pain, he felt weak and perspired profusely. His wife could hear a peculiar sound and upon placing her hand on his chest, felt a "crawling" sensation. When examined, the patient had a grade-VI systolic murmur at the apex accompanied by a thrill. The electrocardiogram showed evidence of subendocardial infarction. The patient survived this episode but died suddenly in his sleep 9 months later. Although the diagnosis of ruptured papillary muscle cannot be proved because an autopsy was not obtained, the figure is consistent with the diagnosis and at least illustrates the type of murmur with sudden onset that should arouse the suspicion of a ruptured papillary muscle or perforation of the interventricular septum.

Rupture of the Ventricle

This complication usually occurs between the second and twelfth day after infarction. Again the murmur is loud and systolic in time and accompanied by a thrill.[14] Cardiac tamponade and rapid deterioration are the consequence.[15]

Ventricular Aneurysm

Although various murmurs have been reported in cases of ventricular aneurysm following myocardial infarction, in our experience most of these cases have no unusual auscultatory findings and the diagnosis is best made by electrocardiography and cardiac fluoroscopy.

Other Murmurs Encountered in Arteriosclerotic Heart Disease

There are other murmurs that may at times be most confusing in a patient with arteriosclerotic heart disease with or without acute myocardial infarction. One of these (fig. 2) is a diastolic murmur, often with presystolic accentuation, which is very similar to the murmur of mitral stenosis. The figure illustrates the stethogram from the cardiac apex of a 48-year-old woman with previous authenticated myocardial infarction who showed progressive cardiac enlargement and cardiac failure but gave no history of angina pectoris. At autopsy there was left ventricular hypertrophy and dilatation and severe coronary atherosclerosis with an old myocardial infarction. The valves were essentially normal, and it is presumed that the murmur resulted from relative mitral stenosis due to dilatation of the left ventricle. It will be noted that there is no opening snap, which would be common in mitral stenosis. Instead there is a low frequency sound which would be consistent with a third heart sound, which is commonly seen

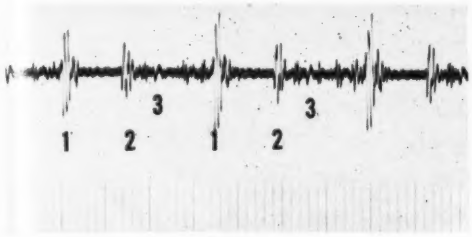

Figure 2

Sphygmogram recorded from the apex of a 48-year-old woman with a history of previous myocardial infarction, increasing cardiac enlargement, and cardiac decompensation but without angina pectoris. The first and second heart sounds are identified. Note the vibrations occurring during diastole including a low-frequency sound, which is probably a third heart sound. This murmur sounded like the low-pitched rumble of mitral stenosis. Time intervals are 0.04 second.

with left ventricular dilatation and in the presence of cardiac failure is interpreted as a gallop sound. When this patient was first seen, the diastolic murmur was wrongly interpreted as evidence of mitral stenosis.

Rheumatic valvular lesions in the older age groups may frequently pre-exist in patients with myocardial infarction and cause great confusion if they have not previously been known. A particularly common variety is aortic stenosis, which is a frequent precursor of angina pectoris and myocardial infarction. We recently had this brought to our attention when we saw a 58-year-old man for the first time who gave a history of severe precordial pain of several hours' duration and in whom the electrocardiogram showed S-T segment changes presumed to be the result of acute subendocardial myocardial ischemia or infarction. While he did have a faint systolic murmur at the aortic area, no great significance was attached to it until he had been hospitalized for a few days. Then it became apparent from the lack of clinical and laboratory signs of acute myocardial infarction and a stable electrocardiogram that the condition was in reality one of previously undiagnosed aortic stenosis with an anginal syndrome. The carotid pulse curve[16] was typical of hemodynamically significant aortic stenosis, and the electrocardiographic pattern was evidently the result of left ventricular hypertrophy.

One could cite many examples of this sort but the variability is extreme and taxes the ingenuity of the physician.

Summary

The auscultatory findings in acute myocardial infarction and arteriosclerotic heart disease have been briefly reviewed. It has been pointed out that there are no auscultatory findings that can equal the efficiency of the electrocardiogram in the diagnosis of acute myocardial infarction. The signs that do occur are probably the result of variable factors such as diastolic filling and ventricular ejection time and are not necessarily peculiar to myocardial infarction. On the other hand, certain complications that may occur as the result of myocardial infarction and certain conditions that may simulate myocardial infarction may produce auscultatory findings that are of definite diagnostic and prognostic significance.

Summario in Interlingua

Es presentate un breve revista del constatationes auscultatori in infarcimento myocardial acute e morbo cardiac arteriosclerosis. Es signalate que il existe nulle constatationes auscultatori que es equal in lor efficacia diagnostic al electrocardiogramma in casos de acute infarcimento myocardial. Le signos que es notate in le auscultation es probabilemente le resultato de varie factores, como replenamento diastolic e tempore de ejection ventricular, e non es necessarimente peculiar a infarcimento myocardial. Del altere latere, certe complicationes que pote occurrer como le resultato de infarcimento myocardial e de certe conditiones capace a simular infarcimento myocardial. produce in certe casos constatationes auscultatori que es definitemente de signification diagnostic e prognostic.

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Diet and Coronary Artery Disease

By ROBERT E. OLSON, PH.D., M.D.

ATHEROSCLEROSIS of the coronary artery is currently the leading cause of death in the United States and in many western countries. It is remarkable that a disease that was not recognized clinically before 1912[1] could have in half a century come from this relative obscurity to the commonest cause of death in middle-aged and elderly persons. Although its exact etiology is far from settled, intensive study over the past three decades has pointed increasingly to nutritional factors as playing a prominent role.

The concept of any disease arising from a single cause is obsolete and misleading. On the contrary, as Gordon pointed out, "To recognize a disease as the resultant of ecologic forces within the dynamic system made up of agent, host, and environment may often clarify our concepts of that disease."[2] Atherosclerosis is undoubtedly a disease of multiple causation, which appears to have so many determinants that they tend to defy orderly classification under titles of agent, host, and environment. It is certain that atheroma arises within the host as the result of a complex interaction between host and environment. Instead of arising in the environment and constituting an independent variable such as the agents of infection, allergy, poisoning, addiction, or vitamin deficiency disease, the agent of atherosclerosis is an endogenous and dependent variable. Since this agent arises within the host, it obscures the usual distinction that is made between agent and host response.

Nevertheless, it seems to me that it is important to postulate an agent, if possible, for this disease, in order to formulate concepts useful for further research on pathogenesis as well as prevention and control. Groups of host factors definitely involved in the pathogenesis of atherosclerosis may be grouped into (a) humoral and (b) local factors.[3] The humoral factors include the lipoproteins of plasma, the heparinoid substances involved in clearing of lipid from the blood, and possibly other plasma proteins concerned with coagulation. The last group of proteins may have more to do with the pathogenesis of thrombosis than with atheroma itself. Under local factors, i.e., those promoting atherogenesis as a result of influencing the condition and function of the artery itself, one can identify (a) hemodynamic factors relating to blood flow, turbulence, and pressure; (b) metabolic factors intrinsic in the arterial tissue; (c) structural factors relating to differentiation of intima, internal elastic membrane, and other components of the arterial wall; and (d) traumatic factors relating to injury, ulceration, and repair. Environmental factors known to influence one or more of these conditions within the host include such variables as diet, drugs, exercise, occupation, culture, and climate. Factors intrinsic to the host that may also modify the humoral and local factors leading to atherogenesis include genetic constitution, age, sex, endocrine balance, and psychic state. The problem centers about the sorting of this welter of factors into more conventional packages labeled agent, host, and environment.

Do we have sufficient evidence to name the agent of atherosclerosis? If we do, it seems useless to continue to visualize the pathogenesis of this illness as being the random com-

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bination of a large variety of endogenous and exogenous factors. In a system of multiple etiology, the agent is only one cause. It must, however, be an essential cause. It would be impossible, for example, to visualize the occurrence of tuberculosis in the absence of the tubercle bacillus, although easy to visualize its nonoccurrence in the presence of the bacillus. Thus, the agent must be an essential, though not necessarily a sufficient cause. The agent for atherosclerosis is unique only in the sense that it arises within the host and becomes a threat to the host as a part of his internal instead of external environment. In my opinion the evidence is at hand to name the β-lipoproteins as the agent for atherosclerosis, and this view may be defended according to Koch's postulates.[4]

The dose of an agent may or may not be the determining factor for disease causation. In man on an abundant diet the β-lipoprotein concentration may be a less important variable in causing overt disease in given individuals than hypertension, tortuosity of vessels, or hereditary predisposition to the degeneration of vascular connective tissue.

If one accepts this evidence in favor of the view that the plasma β-lipoproteins can be considered the agent for atherosclerosis, all other factors known to be involved may be viewed to determine whether they influence the concentration of the agent in the plasma or whether they influence the reactivity of the arterial wall to the agent. Host and environmental factors may then be grouped according to the following epidemiologic triangle (fig. 1).

Since the β-lipoproteins are known to be synthesized in the liver,[5] this organ can be regarded as the source of the agent.

An understanding of the pathogenesis of a given disease is essential to its successful prevention. An ecologic view is important in determining a strategy of attack upon the causes. In coronary artery disease there is little doubt that hypercholesteremia (as a sign of hyper-β-lipoproteinemia) and hypertension[6, 7] are contributory factors. There is a considerable controversy about the role of obesity.[8–11] Since both hypercholesteremia and

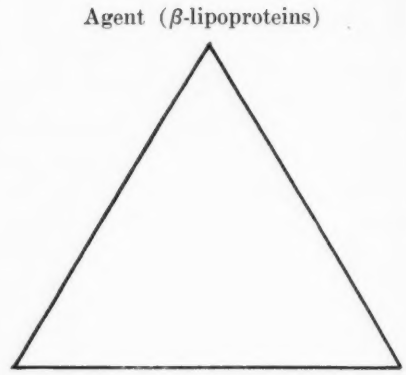

Figure 1

obesity may result from overnutrition, the possibility of a dietary approach to prevention of atherosclerosis must be carefully evaluated.

The evidence supporting a relationship between diet and coronary artery disease rests upon 3 pillars. These are (1) epidemiologic studies of populations differing widely in disease prevalence and correspondingly in nutritional, socioeconomic, cultural, and other environmental status; (2) clinical investigations of small groups of subjects fed carefully controlled diets under the conditions of the metabolic ward; and (3) laboratory investigations of the effect of various purified diets upon serum cholesterol, β-lipoproteins, and atheromatosis in a variety of experimental animals. This evidence is summarized below under these headings:

Epidemiologic Studies

Many studies of diet in relation to mortality for degenerative heart disease[12, 13] have shown that populations that have high rates of coronary artery disease have high mean serum cholesterol and β-lipoprotein concentrations and eat diets rich in animal protein, fat, and calories. This seems to be a real asso-

ation despite differences in diagnoses and porting in various parts of the world. Yerushalmy and Hilleboe[14] and Yudkin[15] have presented data suggesting a stronger association between dietary animal protein intake and mortality from coronary heart disease than between dietary fat intake and that mortality. The association between animal protein intake and mortality for coronary disease may in part reflect the association of relatively saturated fat with most animal protein[16] as well as a possible "protective" effect of animal protein-lack at the low end of the scale.[17] A relative lack of association of dietary fat intake with coronary morbidity and mortality appears at high levels of fat intake. Bronte-Stewart[18] has shown, however, that if one plots the hard fat:liquid fat ratio (as a crude index of relative saturation) against coronary mortality in men 55 to 59 years of age for countries consuming between 100 and 140 Gm. of fat per capita per day, a remarkable parallelism emerges.

Study of populations living with contrasting dietary patterns in the same community has shown that dietary pattern correlates closer with serum cholesterol level and incidence of coronary artery disease than any other environmental variable. The study of Bronte-Stewart, Keys, and Brock[19] of the Bantu, Cape colored, and Europeans living in Capetown, South Africa, is now well known. Toor et al.[20] have made similar observations on the mixed population of Israel. Gupta, Iyer, and Nath[21] have found that patients with coronary artery disease in New Delhi have significantly higher serum cholesterol levels than healthy urban Indians matched for age and occupation. Groen [22] has noted that Trappist monks, who are strict vegetarians, have lower serum cholesterol than Benedictine monks, who eat a more varied diet. Keys and associates[23, 24] have shown that Japanese living in Japan, Hawaii, and Los Angeles have serum β-lipoprotein cholesterol values and coronary mortality in proportion to their intake of fat calories, which were respectively, 13, 32, and 40 per cent. Studies in Finland[25] have revealed a high mortality and morbidity rate from coronary artery disease in that country, a high mean serum cholesterol (260 mg. per cent), and a diet with 35 per cent of calories from fat, most of which is saturated.

Coronary artery disease appears to correlate better with serum β-lipoprotein concentrations and dietary fat intake than other forms of atherosclerosis, suggesting that the coronary vessels are particularly prone to atherogenesis under conditions favored by overnutrition and possibly other factors.

Clinical Investigation

No hypothesis supported solely by associations developed in epidemiologic studies is on firm ground. Confirmatory evidence developed in small groups of intensively studied human subjects is essential for the support of such hypotheses. In addition, such clinical investigations enable the investigator to control with better precision a variety of variables and emerge with more specific knowledge of etiologic factors, control of which is impossible in the field.[26, 27] The general hypothesis developed from field studies is:

Diet ⟶ *serum β-lipoproteins (serum cholesterol)* ⟶ *coronary disease rate*

The first part of this hypothesis, developed in the field, has been subjected to study on the metabolic ward. In more specific form, this hypothesis is:

Δ *Diet* —(1)→ Δ *serum β-lipoproteins*
Metabolic ward studies

—(2)→ Δ *coronary disease rate*
Controlled population study

Examination of the second part of this relationship will require additional study of part one, particularly a study of the practicality of achieving dietary control away from the metabolic ward. Then, a specially designed field study involving relatively large numbers of middle-aged men will have to be carried out to determine if any change in clinical morbidity follows alteration in serum cholesterol and β-lipoproteins by dietary means.

Studies of Diet

Effects of diet on serum cholesterol and β-lipoproteins are discussed under (a) calories, (b) fat, (c) protein, (d) other factors. In a

consideration of the effects of variation of the major constituents of the diet (calories, fat, protein, and carbohydrate) upon the concentration of plasma β-lipoprotein, it is important to remember that variation of one of these variables causes a change in at least one other. In view of the extent to which given foods vary in their total nutrient content, variation in diet sufficient to cause a variation in the intake of a major constituent will usually cause a change of several dietary variables. Further, in epidemiologic studies in which comparisons of dietaries are made it is virtually impossible to obtain "paired" populations subsisting on diets differing in only two of the many possible dietary variables. Hence attempts to interpret the effect of changes in dietary composition upon the concentration of plasma lipoproteins in man must be reserved for well-controlled laboratory studies.

In the ensuing section the effect of variation of calories, fat, protein, and other dietary factors upon postabsorptive plasma cholesterol, and β-lipoprotein levels are discussed. In any discussion of dietary variation (△diet), a statement regarding the baseline from which the variation is to be measured is essential. Although arbitrary, the baseline from which the changes will be computed on this paper is the "average American diet" containing calories to maintain weight (regardless of the weight of the individual) and a distribution of nutrients as per cent of calories as follows: (protein 15 per cent; fat 40 per cent; and carbohydrate 45 per cent; summarized P 15, F 40, C 45). This method of expressing nutrient intake of course is not complete. The specific amino acid pattern of the protein, the specific fatty acid pattern of the fat, and the specific combination of sugars and polysaccharides must also be defined for complete information.

A. Calories

In starvation the body depends mainly upon fatty acids as the source of energy. Triglyceride stored in the adipose depots provides these fatty acids, since lipogenesis in adipose tissue and liver ceases under these conditions. Fatty acids are transported from the depots to various organs in the form of nonesterified fatty acids,[28] and this flow of substrate can account for the total energy expenditure by the fasting man. Most observers agree that there is a small but an undramatic increase in β-lipoprotein concentration in human subjects fasted for periods in excess of 2 days, of the order of 20 per cent with a lesser increase in serum cholesterol, since about half the increase is in the very low density protein.

The feeding of insufficient calories for maintenance of body weight (reducing diets) in man appears to have somewhat different effects upon the level of plasma lipoproteins than in complete starvation even though mobilization of depot fat also occurs in this situation. In Keys' study of semistarved normal young men, it was found that subsistence on diets containing half the caloric requirement resulted in slight but significant fall in average total serum cholesterol from 169 to 151 mg. per cent.[29] Walker et al.[30] found a slight decrease, 14 mg. per cent of serum cholesterol in middle-aged obese subjects offered a 1,000-calories diet containing 50 Gm. of fat over a 4-month period. Olson[31] noted no permanent change in the serum cholesterol concentration of 61 obese men and women losing an average of 20 pounds over a 1-year period after these individuals had attained caloric equilibrium at a new and lower weight. Most of these patients did have transitory decreases during the period of rapid weight loss but these were not sustained. It would appear that weight reduction *per se* and hypocaloric diets approaching the original *ad libitum* fare in the distribution of major nutrients causes little or no change in β-lipoprotein configuration of serum after attainment of the new and lower weight. More marked changes can occur during the early phases of negative caloric balance. These decreases are primarily in the triglyceride-rich low-density fractions of the β-lipoprotein spectrum.

B. Dietary Fat

The simplest variation in dietary fat is a variation of fatty acid composition of the fat

without a change in the total fat intake. In 1952, Groen and associates[32] observed that vegetarians had considerably lower serum cholesterol values than nonvegetarians. This effect was independent of the level of total fat ingested. Independently in the same year, Kinsell et al.[33] observed that the isocaloric substitution of vegetable oil for animal fat in the diet of patients on measured dietary intakes dramatically reduced the serum cholesterol and phospholipids concentrations. These observations were further extended and confirmed by the elegant studies of Ahrens and his collaborators,[34, 35] employing a formula by which a variety of fats at a constant level (P 15, F 40, C 45) were fed to subjects on a metabolic unit for periods up to 3 years. These and other studies[36–40] established beyond question that isocaloric substitution of unsaturated vegetable oils for animal fats and saturated vegetable fats in the diet of man resulted in the fall of serum cholesterol and other lipids of the order of 20 per cent.

It is now clear that the terms "animal" and "vegetable" do not distinguish between fats that raise and lower serum lipids. Both butter and coconut oil raise serum cholesterol, whereas both corn oil and whale oil lower it.[18] Furthermore, the terms "saturated" and "unsaturated" are not suitably descriptive of opposites, since neither all saturated fatty acids nor all unsaturated fatty acids are identical in their effects upon serum cholesterol in man.[18, 41, 42] The dietary fats containing saturated fatty acids in the range of C_6 to C_{14} appear to cause more hypercholesteremia than saturated fatty acids in the range C_{16} to C_{20}.[35, 43] On the other hand, monoethenoid fatty acids such as oleic are not so potent in inducing hypocholesteremia as linoleic, linolenic, arachidonic, and the highly unsaturated fatty acids of fish oils.[39, 44, 45] Finally, the terms "nonessential" and "essential" do not distinguish the serum cholesterol-altering capacities of the various polyunsaturated fatty acids. Both linoleic acid,[44] which is essential for preventing dermal signs and preserving efficiency of food utilization in rats[46] and infants,[47] and linolenic acid,[40] which is nonessential, have potent hypocholesteremic properties. Furthermore, the fish oils contain a large variety of polyunsaturated fatty acids that are nonessential and share the 3, 6, 9 triene moiety (counting from the methyl end) with linolenic acid, and are potent in lowering serum cholesterol in man.[36, 48]

The precise mechanism by which polyunsaturated dietary fat lowers β-lipoprotein and cholesterol concentrations in the serum is not completely elucidated at this time although a variety of studies suggest that the polyunsaturated fatty acids promote the elimination of free cholesterol (which is in equilibrium with plasma free and ester cholesterol) from the liver as neutral sterol and bile acids.[49–51]

A reduction in the level of relatively saturated fat in the diet from 40 to 10 per cent of total calories without changing its fatty acid composition at a constant protein intake results in a decrease in the total serum cholesterol, phospholipid, and S_{f0-12} lipoproteins and an increase in total triglycerides and $S_{f12-400}$ lipoproteins. In normal cholesteremic men the decrease in serum cholesterol and phospholipid is about 15 per cent and the increase in triglycerides is about 50 per cent. The net change in total β-lipoproteins is nil although there is a change in the distribution of lipoproteins of various densities as indicated. In epidemiologic studies of various populations,[23] the plot of mean plasma cholesterol content versus per cent of total calories from a dietary fat, gives a slope that is twice as great as a plot slope of the same line obtained in the study of well-controlled patients in the United States.[52] It seems likely that factors other than the dietary fat level are operating in the populations studied epidemiologically. Low-fat diets reduce the fecal neutral sterol excretion.[53] Varying the content of saturated dietary fat has no effect upon the bile acid output, and it appears that reduced hepatic synthesis of cholesterol may be the primary cause of the reduction of S_{f0-12} lipoproteins and of serum cholesterol in human subjects on low-fat diets.

C. Protein

Description of diets in terms of protein content alone is inadequate and should include

a statement of the distribution of the essential and nonessential amino acids in that protein. Of the 20 amino acids in the common dietary proteins, 8—methionine, valine, tryptophane, leucine, isoleucine, lysine, phenylalanine, and threonine—are required by adult human beings in specified amounts, and, in addition, histidine is required by infants. In general, animal proteins contain amino acids in proportions resembling those found in the tissues of man, and hence have a higher biologic value for man than vegetable proteins, which may not resemble animal tissues in amino acid composition. Some vegetable proteins are actually deficient in certain essential amino acids such as methionine, isoleucine, lysine, tryptophane, and threonine. For these reasons populations living on an exclusively vegetable protein diet are more likely to be marginal in amino acid nutrition than populations subsisting mainly on animal proteins. The requirement for protein of high biologic value by adult humans has been estimated to be from 0.4 to 0.5 Gm. per Kg. of body weight.[54] At energy expenditures associated with sedentary activity this represents about 5 per cent of the calories. No population studied thus far has been found to subsist on such a meager intake although populations living exclusively on vegetable protein have developed protein deficiencies on intakes representing twice this or 10 per cent of calories. The generous recommendation of the National Research Council of 1 Gm. per Kg. per day of good quality protein for adults represents only 11 per cent of calories at a sedentary level of activity.

Our understanding of the effects of a reduced level of dietary protein from 15 to 4 per cent of calories is considerably less specific and complete than the effects of alteration of dietary fat over the same proportional range in man. Kempner and others[55, 56] observed marked hypocholesteremia in patients fed the rice diet, which is low in protein (25 Gm.) and fat (5 Gm.). Since this effect upon serum cholesterol was out of proportion to the effects observed in subjects fed diets low in fat but replete with protein, Olson et al.[17] undertook a series of studies to determine the effect of low-protein diets upon the serum cholesterol and β-lipoproteins in man. Middle-aged human subjects were fed a control ration containing 100 Gm. of protein, 80 Gm. of relatively saturated fat, and 320 Gm. of carbohydrate (P 16, F 30, C 54) for periods of 1 to 4 weeks. Isocaloric substitution of carbohydrate for 75 Gm. of protein yielding a diet containing 25 Gm. of protein (P 4, F 30, C 66) resulted in an average fall in serum cholesterol 44 ± 4 mg. per cent (15 per cent) over a 1- to 4-week period. The fall was sustained as long as 10 weeks. All of the essential amino acids except methionine were supplied by the 25 Gm. of vegetable protein in amounts meeting Rose's tentative minimum requirements[57] although these may be low when several amino acids are at borderline levels. The fatty acid pattern was kept constant, and fiber was kept in the range of 5 to 7 Gm. per day in both diets. Serum β-lipoproteins of the $S_{f0\text{-}12}$ class decreased about 25 per cent, with lesser changes in the lower density groups $S_{f12\text{-}400}$.

Furman, Howard, and Norcia[58] have also recently reported that isocaloric substitution of carbohydrate for all the protein in formula diets fed to adult men caused a marked decrease in serum cholesterol and β-lipoproteins. These workers noted further that this effect was in addition to the effect of polyunsaturated fats, since the basal formula employed used corn oil furnishing 40 per cent of calories.

Severe protein malnutrition in infants characterized by weakness, weight loss, wasting, edema, hypoalbuminemia, hepatomegaly, gastrointestinal mucosal atrophy, and negative nitrogen balance is known as kwashiorkor. This appears to be a multiple amino acid deficiency, a disease in which one or more amino acids may be limiting. In this disease the serum lipids are low (cholesterol – 80 mg. per hundred ml. or less and both α- and β-lipoproteins are decreased).[59-61] The hypocholesteremia of the child with kwashiorkor responds promptly to the feeding of fat-free milk proteins and suggests strongly that dietary fat is not the critical nutrient related to this hypocholesteremia. In fact, it supports

the view that serum lipoproteins are not elaborated by the human at normal rates in the presence of protein deficiency.

Hebrell and co-workers[62] have found in a nutritional survey in Haiti that marked hypocholesteremia was seen in a population subsisting on a diet deficient in protein but moderate in fat (P 9, F 21, C 70).

It appears from both these field and clinical investigations that animal protein intake may become limiting for formation of β-lipoprotein and that in conditions of protein deficiency the serum cholesterol may be depressed on this basis alone.

D. Other Dietary Factors

Dietary carbohydrate appears to exert an influence upon lipoprotein concentrations in two ways. The first is by providing glucose for absorption and metabolism by tissues concerned with lipid storage and transport. The second is by modifying the bacterial flora of the gastrointestinal tract, thereby altering the bacterial metabolism of sterols and bile acids. The first effect varies reciprocally with the level of dietary fat or protein or both, and has been discussed in relationship to the variations of these nutrients in previous sections. In general, low-carbohydrate intakes are associated with the reduction of serum triglycerides and low-density $S_{f12-400}$ lipoproteins and high-carbohydrate intakes are associated with an elevation of triglycerides and low-density β-lipoproteins. The second effect relates to the diversion of metabolites of cholesterol from the enterohepatic circulation by oxidations carried on by intestinal microorganisms. This subject has recently been reviewed by Portman and Stare.[63]

Evidence that the intake of vitamins and minerals within the ranges encountered in populations influences the concentration of serum lipoproteins is not impressive. Two surveys by the Interdepartmental Committee on Nutrition of National Defense[64, 65] failed to show any relationship between specific vitamin deficiency and serum cholesterol. Certain pharmacologic effects of niacin have been reported that are not in this province of discussion. Niacin in doses of 1 to 6 Gm. causes a significant hypocholesteremic effect in man[66, 67] and the corresponding large excretion of nicotinuric acid.[68] It has been suggested that the mechanism of this effect might be via the diversion of coenzyme-A from cholesterol biosynthesis to the CoA-dependent glycine conjugation of nicotinic acid to yield nicotinuric acid.[69] Further evidence is needed to support this interesting hypothesis.

Laboratory Investigation

The study of atherosclerosis in experimental animals has both aided and hindered the development of accurate concepts regarding the role of various etiologic factors in human atherosclerosis. Species variation in responses of animals to a variety of experimental procedures has become evident to most investigators. The evaluation of the enormous bulk of experimental data and particularly its relevance to the human problem can be simplified, in my opinion, by looking at the problem of pathogenesis in animals in the light of a 2-step reaction as in the case of man, viz. (1) effect of variations in diet and metabolic status upon serum cholesterol and β-lipoprotein concentration, and (2) the effect of increased β-lipoprotein concentrations upon the condition of arterial vessels.

In 1913 Anitschkow[70] observed that the feeding of a diet rich in cholesterol to rabbits resulted in experimental atheromatosis. Since that time innumerable experimental animals have been used to study the problem. It has been discovered, however, that not all animals react with hypercholesteremia to cholesterol feeding. In fact most common laboratory animals (rat, mouse, dog, cat) unlike rabbit and chick but, like man, resist hypercholesteremia when simply fed cholesterol; other measures must be employed to alter metabolism in order to obtain elevated serum cholesterol and β-lipoprotein values. Thyroid ablation (chemical or surgical) or cholic acid feeding (which increases cholesterol absorption and retards the conversion of cholesterol to cholic acid) must be added to the cholesterol feeding regimen in order to obtain appreciable hypercho-

lesteremia. Once hypercholesteremia of sizable magnitude is obtained, however, *de novo* atheromatosis occurs in *all* species examined. The problem, therefore, is overcoming the control mechanisms that guard the serum cholesterol concentration. Once this is done the problem may be studied in the experimental animal. Even myocardial infarction has been produced in the rat with massive hypercholesteremia.[71]

The role of specific dietary fats in the control of hypercholesteremia in animals is also somewhat different from that in man. In rat, dog, chick, and rabbit the feeding of large amounts of polyunsaturated fat in the absence of dietary cholesterol exerts no appreciable effect upon the serum cholesterol level; in the presence of cholesterol the effects are not identical to those observed in man.[72]

In general, animal experimentation supports the basic hypothesis previously alluded to. First, diet *can* influence the serum cholesterol and β-lipoprotein concentration in experimental animals. Second, when the β-lipoprotein is high enough, atherosclerosis will develop in a previously normal artery.

From the total of epidemiologic, clinical, and experimental data, it appears that one must accept the fact that diet plays a role in human atherosclerosis. It is certainly not the only factor, and in many cases it may be a minor factor. Furthermore, it must be remembered that clinical disease associated with atherosclerosis is a complication of the basic process in which other factors that may precipitate thrombosis play an important part. The problem of studying this disease in man, therefore, is made difficult by the multiple etiology of atherogenesis plus the multiple etiology of thrombosis. These difficulties, however, should not obscure our vision to the facts that have *emerged* regarding the role of diet in atherogenesis.

With this information about dietary factors in mind, is it possible to elaborate a practical program of preventive medicine against atherosclerosis at this time? Although our knowledge of all the factors operating in the process of atherogenesis is incomplete, our understanding of some of the factors is advancing in an encouraging way. Although it is not possible to eradicate the agent (plasma β-lipoproteins) of this disease, it is possible through appropriate diet therapy to modify the concentration. It remains to be shown, as indicated above, that when β-lipoprotein concentrations of a large number of persons living under conditions of western culture are lowered through appropriate diet therapy, this change will modify their morbidity and mortality from clinical coronary disease. Nevertheless, the evidence is convincing enough at this time, in my opinion, to advise patients with coronary proneness as evidenced by a positive family history and elevated concentration of cholesterol or a disease such as diabetes or hypertension, to follow appropriate diet therapy in the hope that lower serum cholesterol values will improve the prognosis.

The probability of materially influencing the course of coronary artery disease after the occurrence of myocardial infarction is, in my opinion, somewhat less. Nevertheless, clinical judgment must be utilized in recommending diet therapy to such patients in the hope of reducing the rate of recurrence. The studies of Morrison[73] are suggestive although not conclusive that indeed this might be the case.

Summario in Interlingua

Es postulate que un factor particular pote esser designate como le agente de un morbo si il es possibile demonstrar que illo representa un causa essential (ben que non necessarimente sufficiente) del morbo in question. Le autor presenta su conviction que in iste senso le lipoproteinas beta pote esser considerate como le agente de atherosclerosis. Sub iste assertion ille trova possibile classificar le componentes del systema dynamic del multiple causation de atherosclerosis in duo columnas. In le columna de elementos associate con le hospite (i.e. le patiente) ille lista le etate, le function del hepate, le reactivitate arterial, le stato hemodynamic, le stato endocrin, e le stato psychic. In le columna de elementos ambiental, dieta, drogas, exercitio, occupation, cultura, e stress es listate.

Le evidentia supportante un relation inter dieta e morbo de arteria coronari es revistate in tres partes. Istos es: (1) Un discussion de studios epidemiologic de populationes a marcate differentias in le prev-

lentia del morbo e correspondentemente in lor stato nutritional, socio-economic, cultural, e alteremente ambiental. (2) Un discussion de investigationes clinic de iniere gruppos de subjectos recipiente cautemente regulate dietas sub le conditiones del sala metabolic de un hospital. E (3) le discussion de investigationes laboratorial relative al effecto de varie purificate dietas super le cholesterol seral, le lipoproteinas beta, e le genese de atheromatosis in diverse animales experimental.

Super le base de iste revista le autor conclude que il es possibile modificar le concentration de lipoproteinas beta, reguardate como le agente de atherosclerosis, per le prescription de un appropriate therapia dietari—isto in despecto del facto que le multiple aspectos de linteressate campo causal es certo non completemente clarificate. Le prova practic de iste prediction remane a obtener e etiam le prova que le reduction del lipoproteinas beta in un considerabile segmento del population resulta in un correspondente reduction del mortalitate per morbos del arteria coronari.

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Hormones, Cholesterol, and Coronary Atherosclerosis

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RECENT monographs and a rapidly expanding literature[1–4] indicate the interest and large amount of experimental work on the effects of hormones on lipid metabolism and atherosclerosis. The present paper reviews some of these data not with the purpose of dealing exhaustively with the available information but rather to provide the reader with a digestible summary.

The Thyroid Gland

Myxedema is frequently cited as a condition demonstrating a relation between hormonally induced hypercholesteremia and atherosclerosis. Since this presumed relation has been one of the strongest pillars in the hypercholesteremia theory of atherogenesis, the evidence requires careful evaluation.

A wealth of clinical and human experimental observation indicates a potent influence of the thyroid gland on the metabolism of cholesterol and other lipids. Blood cholesterol, serum phosphatides, and fatty acids are increased in myxedema.[5, 6] In cretinous children, a high ratio of free to total serum cholesterol has been described.[7] In adults with myxedema, however, normal or increased ester:total cholesterol ratio occurs. The rise in serum cholesterol is greater than that of phospholipid, and the cholesterol:phospholipid ratio is increased.[8] An increase of low-density (beta) lipoproteins, both in spontaneous and in induced myxedema, is largely in the Sf 0-12 moiety but is found also in fractions Sf 12-400; all of the abnormalities are reversed by the administration of desiccated thyroid.[9, 10] The lipoprotein abnormality may be reversed with very small doses of desiccated thyroid (15 to 30 mg.).[11]

Similar findings are reported in most animal studies: hypercholesteremia accompanies decreased thyroid function whether this results from surgical extirpation,[12] I^{131} radiation,[13] or thiourea administration.[14] The domestic pig is a notable exception.[15] The mechanism of the hypercholesteremia has been explained by studies in animals and man.[16–18] In hyperthyroidism, the serum cholesterol falls in the face of increased cholesterol synthesis, due to increased bile acid excretion (particularly chenodesoxycholic acid). Conversely, in hypothyroidism, cholesterol synthesis is depressed, but bile acid excretion is also decreased; there is a slow turnover of the serum cholesterol, which is elevated apparently because excretion is depressed more than synthesis. Despite the changes in serum cholesterol, available evidence indicates that there is no change in the total body pool of cholesterol in myxedema.

Does myxedema lead to atherosclerosis and is there a relation of the alterations of lipid metabolism in myxedema to atherosclerosis? The evidence is derived from studies of patients with untreated myxedema and cretinism and from studies in experimentally induced hypothyroidism in animals. Since the peak incidence of myxedema occurs at a time when spontaneous atherosclerosis is common, studies attributing atherosclerosis to adult myxedema must be interpreted with caution. Moreover, some of the cases repeatedly cited as evidence for a relation of myxedema to atherosclerosis have been complicated by hypertension and renal disease, conditions which themselves predispose to atherosclerosis.[19] Of interest in this regard is the classic report of the Committee of the Clinical Society of London based on an extensive investigation of the subject of myxedema.[20] It noted that "arterial degeneration, indeed, does not appear to

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exist to any unusual extent, at any rate in the larger vessels." Relevant also are our own studies in adults with rheumatic heart disease and severe congestive failure in whom therapeutic total thyroidectomy was carried out.[21] None of the 8 cases studied by us showed significant coronary atherosclerosis 1 to 13 years after surgical induction of hypothyroidism and its consequent elevated serum cholesterol. Subsequently, careful study with the injection-dissection technic has been made of the hearts of 2 additional patients aged 33 and 45 with multivalvular rheumatic heart disease and chronic congestive heart failure in whom myxedema was induced with I^{131}. Again, despite clear hypothyroidism with elevated serum cholesterol for 1 to 4 years, no complete occlusions or significant coronary narrowing was found. It should be noted, however, that these patients received doses (15 to 30 mg.) of desiccated thyroid, which have been shown to alter serum lipoprotein patterns. These data do not disprove a role of cholesterol in the production of human coronary atherosclerosis. They do suggest that the relation of hypothyroidism to adult atherosclerosis requires further documentation.

The finding of a high incidence of atherosclerosis in young patients with hypothyroidism would offer more substantial support for a relation between these conditions. While clear cases have been reported of extensive atherosclerosis in cretins and patients with juvenile myxedema,[22] such findings are by no means universal. There have also been reported youthful myxedematous subjects in whom no atherosclerosis existed and, indeed, in whom arteries were described as "delicate."[23] It would be of great value to know what factors differentiate the fate of those whose vessels were extensively involved and those free of involvement.

While the clinical evidence correlating myxedema, hypercholesteremia, and atherosclerosis is conflicting, experimental evidence in animals is more consistent. Thus, in rabbits, rats, cockerels, and dogs the combination of thyroid depression (as by thiourea) and cholesterol feeding has usually resulted in atherosclerosis. Indeed, in resistant species, such as the rat and the dog, the addition of thiourea to cholesterol feeding is one of the few methods leading to persistent hypercholesteremia and atherosclerosis.[24] In cholesterol-fed cockerels, hypothyroidism counteracts the ability of estrogens to inhibit coronary atherogenesis.[25] Conversely, thyroid feeding inhibits diet-induced hypercholesteremia and atherosclerosis. Even these experimental data, however, must be regarded with some reservations. Thus, in other studies, feeding thyroid hormones to chicks revealed a conspicuous limitation and inconsistency of its effect. At most hypercholesteremia and atherogenesis were only partially inhibited and in some experiments only minimal effects were noted, despite high dosage. Moreover, large doses of desiccated thyroid inhibited the regression of atherosclerosis that occurs when cholesterol-fed chicks are returned to a plain mash diet. Furthermore, thiourea has been shown to produce more extensive effects than mere thyroid depression; athyreotic thiouracil-treated rats have a higher serum cholesterol than athyreotic controls and liver cholesterol in the former group was 50 per cent higher than in the controls.[1] Finally, while hypercholesteremia in excess of 450 mg. per cent for 1 year appears requisite to atherogenesis, similar hypercholesteremia in I^{131} treated dogs not fed cholesterol does not lead to atheroma formation.[26]

In summary, thyroid depression accompanied by cholesterol feeding will result in marked hypercholesteremia for prolonged periods and atherogenesis in most species. However, mere reduction in thyroid function without cholesterol feeding, yielding only moderate elevation of serum cholesterol, is not a sufficient condition for consistent atherogenesis. Thus, the respective roles of hypothyroidism and hypercholesteremia in atherosclerosis remain to be clarified.

The plasma lipid abnormalities that exist in the hypothyroid state are readily reversed by the administration of thyroid. Significant

depression of serum cholesterol, of the cholesterol phospholipid ratio, and of the beta-lipoprotein cholesterol can be noted even after small doses of thyroid that still leave a hypometabolic state. As a natural extension of this observation, efforts have been made to reduce the cholesterol of euthyroid persons with desiccated thyroid. Unfortunately, large doses of up to 325 mg. of thyroid daily are required to produce a persistent reduction in elevated serum lipids.[27] Such large doses of thyroid are not, however, suitable for administration to patients with coronary disease, euthyroid or hypothyroid, because they may increase metabolic requirements enough to reduce exercise tolerance and provoke angina pectoris. Consequently, an intensive search has been made for a thyroxine derivative that would decrease plasma cholesterol without increasing total body (and particularly cardiac) metabolism. Early enthusiasm for the efficacy of Triac, the acetic acid analogue of triiodothyronine, waned when it was shown to precipitate angina pectoris and diminished exercise tolerance although total body metabolic rate remained unchanged.[28, 29] Moreover, the fall in plasma cholesterol produced by Triac in euthyroid hypercholesteremic men with coronary disease could not be maintained even with increased dosage. Other thyroactive agents that have been tried experimentally or clinically include the propionic and formic acid derivatives of thyroxine and triiodothyronine. In myxedematous patients and euthyroid patients with hypercholesteremia, administration of triiodothyropropionic acid in appropriate dosage reduced serum cholesterol up to 32 per cent with increase of basal metabolic rate of only 4 to 7 per cent.[30, 31] Investigation of other compounds such as diiodothyroacetic acid (DIAC), 33′5′ triiodothyronine, and its derivatives is still in the preliminary stages. Since the chief calorigenic activity of thyroxine exists in its l-isomer, it has been suggested that a hypocholesteremic effect without metabolic stimulation might be achieved by the use of the d-isomer. At present, d-thyroxine[32] and d-triiodothyronine are under active study. In appropriate dosage, these agents have some hypocholesteremic effect before elevation of total body metabolic rate. A number of questions, however, remain to be answered with each: 1. In patients with coronary artery disease, is there exacerbation or precipitation of cardiac symptoms with altered cardiac metabolism? 2. What is the degree of reduction of serum cholesterol and does it persist? 3. In the event that a satisfactory answer is found to the first 2 questions, what influence does such a hypocholesteremic effect have on the natural history of atherosclerosis in man?

Sex Hormones

While some doubt exists concerning the influence of altered thyroid state on atherogenesis in man, the evidence is more convincing that the sex hormones play a role in the development of arteriosclerosis, particularly of the coronary arteries. There is a higher incidence of angina pectoris and acute myocardial infarction due to coronary disease in men than in women. The early studies of Schlesinger and Zoll[33] showed a frequency of coronary occlusions in men six times that of women in the age group 40 to 59 and two times in the age group 60 to 79. A larger series of 1,011 consecutive hearts injected, dissected, and x-rayed according to the method of Schlesinger was analyzed by Wessler (personal communication) with respect to the sex and age incidence of coronary artery disease. Approximately 50 per cent of this series had no symptoms referable to the heart, nor was heart disease the cause of death. The percentage of men having complete occlusion of one or more major arteries was twice that of women in the fourth, fifth, and sixth decades but only a third greater in the seventh and eighth decades. An analysis of the incidence of narrowing (where the cross-sectional lumen of the major artery was reduced 50 to 75 per cent) similarly demonstrated a higher frequency in men than in women up to the sixth decade. In the later decades, the incidence in women was equal to that in men.

Several studies have now shown that bi at-

eral oophorectomy in the young woman increases the incidence and severity of coronary artery disease.[34–37] Wuest et al. compared the degree of coronary atherosclerosis in 49 hearts from women bilaterally oophorectomized 2 to 42 years before death to that in 1,200 hearts from men and women of comparable ages and found significantly more coronary sclerosis in the bilaterally oophorectomized woman than in control women, but less than in the control men. It is interesting that only a small percentage of the women had clinical evidence of coronary artery disease. The small series was not unusually weighted with hypertensive patients nor was there any apparent relation of nutrition to the degree of coronary atherosclerosis. While no unusual increase in clinical incidence of diabetes mellitus was observed, the possibility cannot be completely excluded, since glucose tolerance tests were apparently not carried out.

Rivin and Dimitroff[35] studied the arteries of patients who died from cancer, some of whom were treated with estrogens or were subjected to bilateral oophorectomy. They found increased atherosclerosis in the castrated female subjects and decreased coronary atherosclerosis in the men treated with estrogen and in the women with hyperestrogenism. A recent study by Oliver and Boyd[36] of 200 women, who had had a unilateral oophorectomy or hysterectomy with bilateral oophorectomy 20 years before, confirms the influence of bilateral oophorectomy on the development of coronary artery disease. Coronary artery disease had developed in one quarter of the women who had bilateral oophorectomy and in only 1 of 31 patients who had unilateral oophorectomy. An interesting current study in the Bantu provides additional evidence in this regard.[38] The Bantu has been shown to have a low incidence of death from coronary artery disease.[39] There is no sex difference in severity of arteriosclerosis or in mortality rate from vascular lesions. It has been observed that the male Bantu has a high estrogen excretion and a high incidence of gynecomastia and cirrhosis of the liver. Moreover, in the Bantu, cholesterol levels are equal in both sexes and do not rise after the age of 30 to 40. Although atherosclerosis is present and may be severe, acute coronary occlusion occurs infrequently.

In western populations, serum cholesterol in the female is lower than in the male until the sixth decade when cholesterol levels become higher than those of the male.[40] Bilateral oophorectomy results in an elevation of the serum cholesterol and of the cholesterol:phospholipid ratio. Robinson et al. also found an increase in serum lipids after bilateral oophorectomy in patients with overt coronary artery disease.[41]

With the exception of Engelberg and Glass,[42, 43] many investigators have now found that estrogen administration results, in both men and women, in a decrease in serum cholesterol, a decreased cholesterol:phospholipid ratio, a decrease in the beta-lipoprotein cholesterol, and an increase in the alpha-lipoprotein cholesterol.[44–47] The changes in serum cholesterol occur promptly, within 1 or 2 weeks after relatively large doses of estrogen, and are sustained as long as therapy is administered.[48, 49] As noted above, the phospholipid changes are more marked than the cholesterol changes. As with most agents, the cholesterol fall is greatest in those instances in which initial values are highest. Following cessation of therapy, there may be a rebound. Estrogens are also effective in reducing total and esterified cholesterol, phospholipids, triglycerides, and total lipids in idiopathic hyperlipemias.[50]

The mechanism of the estrogen effect in decreasing the serum cholesterol has not been elucidated. In some species, estrogen decreases cholesterol biosynthesis, while in others, a stimulating effect is observed. It is known that estrogen increases thyroid activity and may result in an increased serum protein-bound iodine. In pregnancy, however, there is an increase in serum cholesterol rather than a decrease. Another effect of estrogen is to stimulate reticuloendothelial activity,[51] shown by Friedman, Byers, and Rosenman to have

a significant influence in clearing the blood of cholesterol.[52]

The protective effects of oral or parenteral estrogens in preventing coronary atheromatosis in cholesterol-fed cockerels has been demonstrated by Katz et al. Estrogens induced the following alterations: feminization, increase in the ratio of free to total plasma cholesterol (FC/TC), enhanced hyperphospholipemia with lowering of the ratio of plasma total cholesterol to lipid phosphorus (C/P) to normal levels, depression of alpha-lipoprotein levels, reduction of Sf 20 – 100 + levels, and prevention of coronary atherogenesis without influencing formation of aortic lesions.[3, 25] Estrogen also reversed the coronary lesions induced by feeding cholesterol. Androgen prevented the feminization while not affecting the decreased cholesterol: phospholipid ratio induced by estrogens or altering the protection afforded the coronary arteries.

There are striking species differences in the response of serum cholesterol to sex hormones. The female rat has a higher serum cholesterol than the male; cholesterol levels are higher in the pre-estrous to estrous phase and fall off thereafter.[53] Testosterone lowers the serum cholesterol and other lipids in the female rat. In the male rat, estradiol stimulates cholesterol synthesis and increases serum cholesterol; conversely, testosterone lowers serum cholesterol. Oophorectomy decreases the cholesteremic response of cholesterol-fed rabbits and rats.[54] Testosterone lowers serum cholesterol in female rabbits, whereas estrogen therapy of male and female rabbits fed cholesterol caused an exaggerated rise in serum cholesterol.

In view of such species differences, caution must be exercised in the transfer of any of these results to man. The clinical usefulness of estrogen therapy is limited in man by side effects including gynecomastia, decreased libido, and weakness, with histologic evidence of testicular atrophy and fibrosis.[47, 55, 56] Moreover, such therapy in men who have already suffered one myocardial infarction does not appear to reduce the incidence of angina pectoris or the frequency of a second acute myocardial infarction, nor does it appear to prolong life. In the postmenopausal woman, estrogen therapy has little effect upon serum cholesterol. Further data are necessary, however, to determine the effects of estrogen on vascular disease in such persons. It thus appears that estrogen therapy should be restricted to the young woman in whom bilateral oophorectomy has been performed.

The search for other substances with hypocholesteremic but less estrogenic effect is under active pursuit. One such substance,[57] Manvene (a 3,16-substituted estriol derivative) has less estrogenic side effects, but recent reports indicate that this agent alters liver function significantly. A new agent, MER 29, triparanol, related to TACE, a synthetic estrogen, does reduce serum cholesterol and is without estrogenic effect.[58] It apparently interferes with cholesterol production late in the biosynthetic pathway. An increase in the liver and blood of a cholesterol precursor, 24-dehydrocholesterol or desmosterol, following triparanol therapy has been shown by Avigan et al.[59] Desmosterol gives a color in the Lieberman-Burchard reaction which is less intense than cholesterol. Consequently, the reduction in total serum sterol is less than would be indicated by the standard methods of cholesterol determination. Whether desmosterol has an effect similar to cholesterol on atherogenesis remains to be determined.

The effects of testosterone and related substances on atherosclerosis in man require additional study. Testosterone does not have a favorable effect on angina pectoris; the initial reports indicating benefit have not been confirmed. Although testosterone produces no change in total serum cholesterol, there is a reduction in alpha-lipoprotein cholesterol and an increase in the beta-lipoprotein cholesterol following testosterone or methyl testosterone. The androgens abolish completely the effects of estrogen on serum cholesterol and lipoproteins in man but have very little effect on the feminizing capacity of estrogens.[45] A possible

therapeutic effect of derivatives of androgens is suggested, however, by the data of Hellman et al.[60] They have shown a distinct hypocholesteremic effect following the administration of etiocholanalone and androsterone. Further studies will undoubtedly be forthcoming with these and related substances.

Adrenal Cortex

Evidence of the effects of adrenal cortical hormones on circulating lipid and on the development of atherosclerosis is conflicting. Observations in experimental animals are not in agreement with those obtained in human patients with a variety of pathologic conditions in whom hormones were used for therapeutic purposes. Studies on normal human subjects are limited. Species differences in circulating lipids and lipoproteins limit the applicability of animal experiments to man.[61]

Clinical observation[62] has suggested that hyperfunction of the adrenal cortex (Cushing's syndrome) produces hypercholesteremia and an abnormal distribution of body fat, whereas adrenal cortical insufficiency is associated with a low serum cholesterol and a loss of body fat. Similarly, adrenalectomized dogs maintained on desoxycorticosterone acetate (DOCA) suffer a progressive decrease in plasma phospholipid and cholesterol. The administration of cortisone after DOCA withdrawal has led to a rapid restoration of serum lipids.[63]

However, when either corticotrophin or cortisone acetate was administered intramuscularly to ambulatory men with high plasma cholesterol and coronary artery disease, the plasma cholesterol, the total cholesterol: phospholipid ratio, and beta-lipoprotein cholesterol fell and the alpha-lipoprotein cholesterol rose.[64] Conn and Vogel also showed a drop in serum cholesterol levels during short-term administration of corticotrophin.[65] In contrast, Adlersberg et al.[66] reported that when cortisone was administered to 18 patients severely ill with a variety of clinical conditions, there was an increase of total and esterified cholesterol and phospholipid and a decrease in serum neutral fat. Only 4 of the 18 ill patients had serum cholesterol levels above 250 mg. per cent and, in these, there was no change after cortisone therapy. Bloom and Pierce administered corticotrophin to 9 patients and noted a decrease of serum cholesterol without change in the ester ratio.[67] The effect of cortisone was less consistent. In 6 patients receiving short-term corticotrophin and cortisone therapy and in 8 of 9 patients undergoing long-term cortisone therapy, they noted no trend in Sf 10-20 lipoprotein or serum cholesterol.[68]

In the normal rabbit, administration of corticotrophin and cortisone results in lipemia, increased serum lipoproteins Sf 80-400, and smaller quantities of Sf 40-80. After cessation of cortisone, there is a serial conversion of the larger to smaller lipoprotein until normally occurring Sf 3-12 results. Moreover, the combined administration of cortisone and cholesterol feeding resulted in enhanced levels of all lipid fractions compared with cholesterol feeding alone.[69] In chickens, hydrocortisone and long-acting corticotrophin produced diabetes and enhancement of hypercholesteremia although cortisone was relatively inactive.[70]

Interest in the influence of the adrenal cortex on circulating lipids is enhanced because of the relation of the adrenal cortex to stress. A number of stressful situations (surgery, starvation, infection) in man and animal have been shown to result in a decrease in serum cholesterol.[71] Relief of stress after steroid therapy of serious disease has been suggested as the cause of the resulting rise of cholesterol.[72] On the other hand, an increased serum cholesterol has been shown in medical students at the time of examination and in accountants during tax periods.[73, 74]

The influence of steroids, hypercholesteremia, and stress on human atherogenesis remains obscure. It has been suggested that human beings with hyperadrenocorticism frequently develop premature severe atherosclerosis.[62] If so, the relative role of hypertension, diabetes, and lipids has not been clarified. In the rabbit and chick, the hyperlipemia and

hypercholesteremia occurring after administration of cortisone, hydrocortisone, and corticotrophin has been associated with the deposition of significantly less arterial lipid than in control cholesterol-fed animals.[75] This suggests that in the rabbit other factors (i.e., the state of the ground substance) than hypercholesteremia and its duration exert an influence on atherogenesis. On the other hand, studies in rats suggest that stress may enhance the development of atherosclerosis.[76]

Adrenal Medulla

The effect of stress on serum lipids may be mediated not only through the adrenal cortex but also through the adrenal medulla and the sympathetic nervous system. The effect may be primary or the result of a secondary release brought about by a specific pituitary mobilizing factor.

Norepinephrine and epinephrine increase circulatory levels of free fatty acids in man and in dogs.[77, 78] Prolonged injections of epinephrine result in a rise in serum cholesterol and phospholipid with a smaller and variable response in triglycerides. There is also an increase in the d=1.019 to 1.063 and in the d=1.063 to 1.21 lipoprotein fractions. Both the fatty acid and lipoprotein responses to epinephrine are abolished or markedly reduced in adrenalectomized rats and dogs, and the normal response is restored by cortisone. Thus, increased secretion of both adrenal medullary and cortical hormones may be important in the hypercholesteremia of stress.

Pituitary Gland

Most of the hormones of the pituitary gland exert an effect on lipids through their respective end organs. Thus, the effects of corticotrophin and thyroid-stimulating hormone are considered under the adrenal cortex and thyroid gland. The latter has been shown to have no effect in the myxedematous human.[64] The administration of beef or porcine somatotrophin preparations to man also produces no effect on circulating cholesterol. Recent observations of Seifter and Baeder[79, 80] and by Rudman[81] suggest that fat may be brought into the blood from depots by a pituitary lipid-mobilizing factor separate from the known pituitary hormones.

The effect of pituitary hormones on atherogenesis is unknown. However, in the white female rat, which is notoriously resistant to the development of experimental atherosclerosis, administration of corticotrophin results in explosive atherogenesis, coronary sclerosis, and infarction with lesions strikingly like those seen in man.[82]

Summary

Various hormones have been shown to play an important role in lipid metabolism. Clinical and experimental observations implicate the thyroid, adrenal, gonadal, and pituitary glands in atherogenesis. The evidence is strongest that estrogens play a role in human atherosclerosis. The influence of hypothyroidism requires further study and clarification. Hormones and lipids are obviously not the only factors important in atherogenesis; hypertension, local tissue factors, and altered intravascular coagulation in all probability significantly influence the natural history of the disease.

Summario in Interlingua

Ha essite monstrate que varie hormones ha un rolo importante in le metabolismo de lipidos. Observationes clinic e experimental implica le glandulas thyyroide, adrenal, gonadal, e pituitari in le atherogenese. Le indicios es le plus convincente con respecto al rolo del estrogenos in le genese de atherosclerosis human. Le influentia de hypothyroidismo require studios additional e debe ancora esser clarificate. Hormones e lipidos es obviemente non le sol factores de importantia in le atherogenese. Hypertension, local factores tissutal, e alteration del coagulation intravascular exerce con alte grados de probabilitate un significative influentia super le historia natural del morbo.

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CLINICAL PROGRESS

Metastatic Cancer to the Heart

Review of the Literature and Report of 127 Cases

By STANLEY M. HANFLING, M.D.

METASTATIC cancer to the heart assumes greater diagnostic and therapeutic importance as the incidence of cancer rises. The condition evidently was first described by Boneti in 1700.[1] A report in the English literature appeared in 1822 of a case of testicular cancer with tumor filling the vena cava and extending to the edge of the Eustachian valve.[2] Subsequent reports described metastases to all parts of the heart from many types of cancer arising from almost every organ of the body.[3-8] Characteristically, authors mentioned the paucity or complete absence of symptoms, often despite extensive involvement of the heart by tumor.

The first correct antemortem diagnosis of cancer in the heart was reported in 1913, but not until 1930 did reports of this nature appear in the English literature.[9, 10] Comparatively few articles have been written on treatment and the effects of treatment on cancer metastatic to the heart.[11-13]

Pathology

Neoplastic growths may involve any or all parts of the heart. Most commonly, embolic tumor cells reach the heart by a hematogenous route entering the smaller coronary vessels from which they invade the heart. More uncommonly, fibrin forms on tumor cells freed in the venous system, supporting the further growth of tumor and resulting in a tumor thrombus that may extend into the heart chambers. Tumors may also reach the heart by direct extension from an intrathoracic cancer. Finally, tumor may reach the heart by retrograde flow through mediastinal and tracheobronchial lymphatic channels. Microscopically, the superficial lymph channels of the heart may be filled with malignant cells,[14] a finding known as carcinomatous lymphangitis.

Pathologically, heart metastases are usually small, firm, and nodular, microscopically resembling the primary lesion. Necrosis is uncommon. Leukemia usually causes diffuse and focal infiltrations radiating around blood vessels; in the absence of invasion, leukemic cells may nevertheless be seen in the lumen of smaller vessels. Emboli from cancers of different origin may also be seen occasionally in the lumen of coronary vessels.[15]

Incidence and Data of Observed Cases

There has been a gradual rise in the incidence of cardiac metastases, probably because of the rising incidence of cancer itself in patients living longer with their disease (table 1). The incidence of metastatic cancer to the heart in patients dying of cancer ranges from 1.5 to 13.9 per cent, with a general increase in recent series.

Results

The New York Hospital is a private voluntary hospital. In the 7-year period, 1947 through 1953, 2,652 autopsies were performed. Of these, 694 were deaths from cancer, including 169 cases of lymphoma, leukemia, and myeloma. The 127 cases of metastatic cancer to the heart constituted an incidence of 4.8

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Table 1

Incidence of Metastatic Cancer to the Heart (Collected Series)

Author and reference	Year reported	Total cases	Cancer cases	Heart metastases	Percentage of heart metastases	
					Total cases	Cancer cases
Pic and Bret[16]	1891	—	1708	25	—	1.5
Karrenstein[17]	1908	6655	—	19	.29	—
Symmers[18]	1917	5155	298	9	.17	3.1
Morris[19]	1927	3000	—	5	.17	—
Burke[4]	1934	—	327	14	—	4.3
Lymburner[14]	1934	8550	—	52	.61	—
Helwig[20]	1935	1000	—	9	.90	—
Pollia[21]	1936	12,000	1450	29	.24	2.0
Schnitker[22]	1937	3570	—	19	.53	—
Scott[23]	1939	11,100	1082	118	1.06	10.9
Ritchie[24]	1941	3000	—	39	1.30	—
Herbut[25]	1942	4050	640	35	.87	5.5
Dimmette[26]	1950	1815	455	38	2.11	8.4
Prichard[27]	1951	4375	—	146	3.4	—
DeLoach[28]	1953	2547	980	137	5.3	13.9
Bisel[29]	1953	—	340	37	—	12.1
Gassman[30]	1955	7952	4124	217	.03	

per cent of all autopsies and 18.3 per cent of deaths from cancer. Of 525 deaths from visceral and cutaneous cancers (including brain tumors), 61 showed gross metastases to the heart (tables 2, 3, and 4). Of 169 cases of lymphoma, leukemia, and myeloma, 61 showed metastases to the heart, mostly microscopic (table 5).

Of the 61 cases of gross metastases to the heart from visceral and cutaneous sources, metastases occurred to the pericardium in 36, myocardium and epicardium in 22, and pericardium and myocardium in 2. There was 1 tumor thrombosis. Most patients were in the sixth and seventh decades of life, although the age span was 6 to 83. There were 38 male and 23 female patients in this series.

Two cases showed no metastases elsewhere; the heart was involved by direct extension. In a case of retroperitoneal fibroliposarcoma, the coronary arteries were involved by direct extension of the tumor. The other was an adrenal cortical carcinoma with tumor thrombosis. All others showed metastatic foci elsewhere. Of concomitant metastases, lymph nodes, liver, and adrenal glands were each involved in over 50 per cent of cases, kidney in over 33 per cent, pancreas in over 25 per cent, and thyroid gland in 16 per cent.

Carcinoma of the lung and breast, lymphoma, leukemia, and malignant melanoma spread to the heart with great frequency, although practically all cancers may involve the heart.[23, 31-33] Of 74 cases of leukemia in the present series, the heart was involved in 46 per cent (table 5). Malignant melanoma also has a tendency to invade the heart. Bisel found 15 cases of cardiac involvement in 34 cases.[29]

Metastatic cancer to the heart is usually a late manifestation of cancer and accompanied by foci elsewhere, although, in rare cases, the heart is the sole metastatic site.[25, 34] In most instances the tumor is associated with primary or secondary intrathoracic malignancy. De Loach found this in 136 of 137 cases.[28] Lymburner[14] found it in 88 per cent of his series. In the present series of 61, gross metastatic cancers to the heart, primary or secondary malignancy occurred in 93 per cent. Pollia and Gogol[21] concluded from similar findings that "the presence of primary or metastatic cancer of respiratory thoracic tissues should suggest the possibility of involvement of the heart."

Symptomatology

The symptomatology of heart metastases is variable, depending as much or more on loca-

Table 2

Incidence of Cardiac Metastases from Cancer (New York Hospital Data 1947-1953)*

Type	Number of patients: Total	No. with cardiac involvement†	Percentage
Carcinoma of lung	93	21	23
Carcinoma of breast	24	8	33
Carcinoma of stomach	49	4	8
Carcinoma of pancreas	27	3	11
Carcinoma of bladder	32	3	9
Malignant melanoma	9	3	33
Site undetermined	6	3	50
Mesothelioma of lung	2	2	100
Undifferentiated sarcoma	2	2	100
Neuroblastoma	4	1	25
Adrenal cortical carcinoma	1	1	100
Carcinoma of jejunum	1	1	100
Ewing tumor	1	1	100
Fibrosarcoma of forearm	1	1	100
Retroperitoneal fibroliposarcoma	1	1	100
Carcinoma of gallbladder	5	1	20
Carcinoma of extrahepatic ducts‡	5	1	20
Carcinoma of esophagus	16	1	6
Carcinoma of kidney	15	1	7
Carcinoma of colon	45	1	2
Carcinoma of ovary	28	1	4
Other tumors	158	0	0
Total	525	61	11.6

*Excluding lymphoma, leukemia and myeloma.
†Gross involvement only.
‡Including cancer of common bile ducts.

Table 3

Incidence of Pericardial Metastases from Cancer (New York Hospital Data 1947-1953)*

Type	Number of patients: Total	No. with pericardial involvement†	Percentage
Carcinoma of lung	93	17‡	18
Carcinoma of breast	24	5	21
Carcinoma of pancreas	27	3	11
Carcinoma of bladder	32	2	16
Malignant melanoma	9	1§	11
Carcinoma of esophagus	16	1	6
Carcinoma of stomach	49	1	2
Carcinoma of jejunum	1	1	100
Carcinoma of colon	45	1	2
Carcinoma of ovary	28	1	4
Ewing tumor	1	1	100
Mesothelioma of lung	2	1	50
Fibrosarcoma of forearm	1	1	100
Sarcoma	2	1	50
Undetermined site	6	1	17
Other tumors	189	0	0
Total	525	38	7

*Excluding lymphoma, leukemia and myeloma.
†Gross involvement only.
‡Including one case involving myocardium.
§Involving myocardium also.

tion than on size. Extensive involvement may occur with few or no symptoms.

Yater proposed a classification of the symptomatology in 1931, dividing the symptoms into 2 groups: clinical types suggestive of tumors and types not suggestive (table 6).[35]

This classification does not stress tumor lolation that is responsible in large measure for the symptoms and signs that develop. The outlines in tables 7 through 10 differ in emphasis and are suggested as a supplement to the Yater classification.

Pericardial Involvement

Pericardial involvement may occur alone or may be associated with metastases elsewhere in the heart (table 7). Metastases arise from hematogenous or lymphatic dissemination of tumor. Intrathoracic growths, usually carcinoma of the lung or breast or lymphoma, may extend directly into the pericardium. From the pericardium, the tumor may invade the epicardium, the myocardium, and occasionally the endocardium.

There are usually no symptoms of pericardial tumor.[36] The most common signs of pericardial metastases are pericarditis and pericardial effusion. The effusion may be serous or bloody. The diagnosis of metastatic pericardial tumor has been established in many cases by finding neoplastic cells in aspirated pericardial fluid.[37]

Rarely, tumor involvement causes constrictive pericarditis. Wallace and Logue[38] reported a case of bronchogenic carcinoma with right heart failure a prominent symptom. Electrocardiographic tracings suggested chronic pericarditis. At necropsy, there was extensive infiltration of the pericardium by firm, nodular, tumor tissue which formed a mass 2.5 cm.

Table 4

Incidence of Myocardial (and Epicardial) Metastases from Cancer (New York Hospital Data 1947-1953)*

Type	Number of patients		
	Total	No. with myocardial and epicardial involvement†	Percentage
Carcinoma of lung	93	5‡	5
Carcinoma of breast	24	3	13
Carcinoma of stomach	49	3	6
Malignant melanoma	9	3‡	33
Site undetermined	6	2	33
Cancer of kidney	15	1	7
Carcinoma of extrahepatic ducts	5	1	20
Carcinoma of bladder	32	1	3
Mesothelioma of lung	2	1	50
Neuroblastoma	4	1	25
Retroperitoneal fibroliposarcoma	1	1	100
Sarcoma	2	1	50
Carcinoma of gallbladder	5	1	20
Other tumors	278	0	0
Total	525	24	4.6

*Excluding lymphoma, leukemia and myeloma.

†Gross metastases only.

‡Includes 1 case involving pericardium in addition.

Table 5

Incidence of Infiltration in the Heart from Lymphoma, Leukemia, and Myeloma (New York Hospital Data 1947-1953)*

Type	Number of patients		
	Total	No. with involvement	Percentage
Leukemia†	74	34	46
Lymphomas‡	85	27	32
Multiple (plasma cell) myeloma	10	0	0
Total	169	61	36

*Infiltration mainly microscopic.

†Includes acute and chronic myelogenous, monocytic, and stem-cell leukemia.

‡Includes Hodgkin's disease, malignant lymphoma with leukemia, reticulum-cell sarcoma, and follicular type lymphoma.

Five cases of cancer from visceral or cutaneous sources showed microscopic metastases to the heart.

thick, completely encasing the heart. Slater et al.[39] reported a case of constrictive pericarditis from metastatic breast cancer to the pericardium.

Pericarditis also suggests tumor. Smith[40] reported a case of a patient with malignant melanoma with a pericardial friction rub at the base of the heart. Along the right border was an area of increased density that extended into the pulmonary parenchyma. Necropsy revealed extensive neoplastic infiltration of the pericardium. Levy[41] diagnosed metastasis on the basis of a pericardial friction rub with electrocardiographic evidence of pericarditis in a patient with bronchogenic carcinoma.

The electrocardiogram may be helpful in demonstrating pericarditis, but as Lamberta and co-workers[36] concluded, "... the electrocardiographic changes illustrative of pericarditis are minimal in malignancy of the pericardium unless there is sufficient ... involvement."

Fischer[42] mentioned that the introduction of air into the pericardial sac has been recommended as an aid in delineating the presence or absence of tumor.

Epicardial and Myocardial Involvement

Cancer cells reach the heart most often by the hematogenous route (table 8). From the myocardium, tumor may spread to the pericardium and epicardium. Spread to the myocardium also occurs from retrograde lymphatic flow through bronchomediastinal lymphatic channels and from direct extension from pericardial metastases.

In the past, the low incidence of cancer to the heart has been explained on the theory that the heart was not receptive to tumor cells. Prichard[27] mentioned the kneading action of the muscle, the metabolic peculiarity of striated muscle, and the rapid blood flow as factors accounting for the low incidence. Later authors considered that the low incidence more likely was a result of inadequate observation, and Burnett and Shimkin[43] concluded, "in tumours that have spread beyond the lung and liver filters, there is almost an equal likelihood of the thyroid, the adrenal gland and the heart to be involved with metastases." Both sides of the heart appear to be affected equally.

Generally, myocardial metastases are asymp-

Table 6

Symptomatology of Heart Metastases—Yater Classification

Clinical types not suggestive of tumor to the heart
Absence of symptoms referrable to the heart
Symptoms of cardiac embarrassment terminally
Symptoms of congestive heart failure
Sudden death
Symptoms suggestive of subacute bacterial endocarditis
Clinical types suggestive of tumor of the heart
Heart block
Symptoms referrable to location of the tumor other than heart block
Symptoms of cardiac dysfunction developing without apparent cause in a patient with a known malignant process
Accumulation of hemorrhagic fluid, pericardial and pleural
Suggestive roentgen observations

Table 7

Pericardial Tumor Involvement

Route
Hematogenous
Direct extension from intrathoracic neoplasm
Spread from myocardial and epicardial metastases
Retrograde lymphatic spread from tracheal and bronchomediastinal lymphatic channels
Symptoms and Signs
No clinical manifestations
Pericarditis
Pericardial effusion, serous or bloody
Constrictive pericarditis
Diagnosis
Awareness of presence of intrathoracic neoplasm
Examination of pericardial fluid for malignant cells
X-ray—general enlargement of the heart
Fluoroscopy—fixation of the right border of the heart
Introduction of air into the pericardial sac to outline nodules
Therapeutic test-irradiation of pericardium

tomatic. Symptoms may occur from encroachment on the pericardium, endocardium, or conduction system by infiltration of cancer. In the latter instance, the arrhythmias or rate changes provide important clues for antemortem diagnosis. Doane and Pressman[44] stated that whenever the right heart is involved, the interventricular septum is likely to share in the process and the conduction system is apt to be embarrassed. Arrhythmias may occur, however, without septal invasion.

Tumor nodules in the ventricular muscle mass usually are asymptomatic and do not produce any characteristic x-ray, fluoroscopic, or electrocardiographic signs. Atrial flutter or fibrillation may occur although the mechanism is obscure.

Depending on their location, tumors may cause other symptoms and signs. Tumor emboli occasionally plug a vessel and produce coronary insufficiency, angina pectoris, or myocardial infarction. Pilcher[45] reported a case characterized by clinical electrocardiographic evidence of coronary thrombosis with encroachment or invasion of coronary vessels by malignant tissue at necropsy.

Metastases to the heart may affect the muscle sufficiently to produce congestive failure. Scott and Garvin[23] concluded that the development of congestive failure without apparent cause in patients with malignant disease raises the possibility of cardiac metastases. McNamara and associates[46] reported cardiac rupture from metastatic cancer in a patient with rheumatic mitral disease. At necropsy, rupture of the posterior wall of the left atrium was observed. No other case of cardiac rupture from metastatic cancer has been reported.

The electrocardiogram has been of some help in the diagnosis of metastatic cancer to the heart. Bisel et al.[29] reported that cardiac metastases may cause T-wave changes, S-T deviations, and Q waves. Rosenbaum's group[47] reported a case of esophageal cancer with persistent and pronounced upward displacement of the RS-T segment. Necropsy revealed extensive infiltration of the heart by metastases. Siegel and Young[48] reported a case of lymphosarcoma with inverted T waves and isoelectric S-T segments in all leads. Necropsy revealed tumor in the ventricular wall and interventricular septum. Electrocardiographic changes occur with leukemic infiltration usually when clinical evidence of involvement is present.[49] Occasionally, the electrocardiogram may be the first evidence of myocardial infiltration. As with other cancers to the heart, there are no diagnostic patterns.

Table 8

Epicardial and Myocardial Involvement

Route
Hematogenous
Retrograde from lymphatic-bronchomediastinal channels
Extension from pericardial involvement
Symptoms and Signs
No clinical manifestations
Changes in rate or rhythm
Unexplained tachycardia
Atrial flutter
Atrial fibrillation
Heart block, complete or incomplete
Atrioventricular rhythm
Premature beats
Electrocardiographic changes
Persistent RS-t elevation
Persistent T-wave inversion
Bundle-branch block
low-voltage QRS
Sudden death (severe arrhythmia, heart rupture)
Congestive heart failure
Coronary occlusion
Angina pectoris
Diagnosis
Awareness
Unexplained arrhythmia in patients with cancer
Unexplained electrocardiographic changes in patients with cancer

Table 9

Endocardial Tumor Involvement

Route
Hematogenous to chambers with direct implantation
Extension from myocardial metastases
Symptoms and Signs
No clinical manifestations
Murmurs of stenosis
Sudden death
Diagnosis
Awareness-development of a murmur
Changing murmurs with position
Angiocardiography

Table 10

Chamber Involvement—Tumor Thrombosis

Route
Right heart
Inferior vena cava → right atrium (hypernephroma, testicular tumors)
Superior vena cava → right atrium (carcinoma of lung)
Left heart
Pulmonary veins → left atrium (carcinoma of lung)
Symptoms and Signs
No clinical manifestations
Murmurs of stenosis
Soft heart sounds of poor quality
Superior or inferior vena caval syndrome
Diagnosis
Angiocardiography

The diagnosis of metastatic tumor in the myocardium has usually been made when an arrhythmia develops in a patient with metastatic cancer elsewhere. The first correct antemortem diagnosis of myocardial metastases was reported by Rösler in 1924.[50] The patient had metastatic cancer and developed a persistent slow and regular cardiac rate of 26 to 28 per minute, with an atrial rate of 108. The author ascribed the phenomenon to tumor involvement of the bundle, a diagnosis that was confirmed at autopsy. In the English literature, Willius and Amberg[10] reported the first correct diagnosis, when incomplete bundle-branch block appeared in a patient with sarcoma of the femur. Levy[41] and Fishberg[9] reported patients with bronchogenic carcinoma; cancer of the heart was suspected because of onset of atrial fibrillation, the findings were confirmed at autopsy. Schnitker and Bailey[22] diagnosed a case correctly because the "presence of auricular flutter with the suspicion of bronchogenic neoplasm suggested that there might be encroachment of tumor growth on the right auricle of the heart." Other cases have been reported by Brick and Greenfield,[3] Shelburne and Aronson,[13] and Dresdale and co-workers.[32]

Endocardial Involvement

Neoplastic implantation on the endocardium is uncommon (table 9). Tumor emboli reaching the heart chambers may implant on the endocardium directly with "subsequent development in the direction of least resistance, i.e., out into the cavity and between the muscular trabeculae."[51]

Coller and associates[52] reported there were only 9 cases of tumor deposition on the endocardium in the literature, of which 6 were im-

planted on the valves. He believed a certain amount of valvular damage was necessary for tumor implantation to occur, for it seemed improbable that tumor could implant on an intact cusp with smooth surface. The tricuspid valve or the tricuspid and mitral valves may be involved. Nicholls[53] and Blumenthal and Peterson[34] reported cases with attachment on the surface of the right ventricle. Moragues[54] reported a case of malignant melanoma implanting in the region of the conus arteriosus. The growth, large and pedunculated, almost plugged the pulmonary orifice completely. Watts[55] reported a case in which an intracardiac metastasis probably arose by direct implantation on the wall of the right atrium. Ragle[56] reported a somewhat similar case. Most of the endocardial growths cause little disability during life, and, like most metastatic cancer of the heart, are usually an unexpected and incidental autopsy finding. Endocardial metastases may also mimic bacterial endocarditis.

Chamber Involvement—Tumor Thrombosis

Tumor may invade the heart chambers themselves (table 10); tumor cells that infiltrate the lumen of a great vein may initiate the deposition of fibrin upon them. The fibrin, in turn, serves as a framework for continued cancer growth. This "symbiosis" produces a thrombus in which cancer cells are an integral part. The tumor thrombosis may extend along the vein to the heart chambers, hindering blood flow and effective cardiac action.

Tumor thrombosis of the inferior vena cava and right atrium commonly occurs from cancer of the kidney[57–58] and testes and occasionally the liver,[59] whereas growth into the superior vena cava producing tumor thrombosis to the right atrium occurs from carcinoma of the lung,[60] lymphosarcoma, and cancer of the thyroid gland.[61–62] The left atrium may be invaded from extension of tumor thrombosis of the pulmonary veins, most commonly resulting from carcinoma of the lung.[63, 64] Primary pulmonary sarcoma and osteogenic sarcoma metastasizing to the heart by tumor thrombosis have also been reported.

Murmurs typical of stenosis may be caused by an intracardiac tumor and may change with position. Pedunculated tumor masses may cause considerable interference with blood flow through the heart. Linell[65] reported a case of a patient with carcinoma of the larynx, with a rapidly deteriorating course. At necropsy, a large antemortem clot was found in the cardiac chambers. Upon removal, a pea-sized papillomatous mass was found projecting into the heart cavity from the endocardial wall. The author concluded that the patient's terminal course was precipitated by thrombus formation promoted by the endocardial tumor. The symptoms and signs of venous and intracardiac involvement are often minimal in relation to the extensive involvement seen. Intracardiac involvement may be masked by superior or inferior vena caval syndromes. Tumors may cause valvular murmurs practically identical to those of established valvular disease.

Tumor thrombosis, like metastatic growths elsewhere in the heart, may produce sudden death. Culpepper and Von Haam[59] reported a case of carcinoma of the liver with sudden death shown to have a tumor thrombosis of the inferior vena cava that protruded into the right atrium, which may have caused sudden death by its ball-valve action. Angiography may be valuable in delineating the presence or absence of intracardiac tumor masses.

Treatment of Metastatic Cancer to the Heart

There have been only a few reports of treatment of metastatic cancer to the heart, but successful, though temporary relief, has been given with symptomatic cancer of the heart. Blotner and Sosman[11] reported a case of leukemia with 2:1 heart block, attributed to leukemic infiltration or a leukemic nodule in the bundle of His. X-ray therapy was followed by disappearance of the block for a number of days, with temporary disappearance for a second time after additional therapy.

Shelburne and Aronson[13] reported an instance where a patient with cancer developed heart block with a large pericardial effusion. As a result of deep x-ray therapy, the heart

block disappeared and the effusion resolved completely without discernible adverse effects on the heart. Hsiung's group[12] treated a patient with metastatic tumor to the heart and pericardium with x-ray and found evidence of reduction in heart size and disappearance of the pericardial effusion. They concluded that irradiation can also serve as a therapeutic test and substantiate the diagnosis of metastatic cancer to the heart, if the tumor is radiosensitive. Digitalis may control the arrhythmias so produced, but in some instances,[18] it is ineffectual.

Summary

A review of the literature of metastatic cancer to the heart is presented, and a new classification offered.

Autopsy data of The New York Hospital have been analyzed. In the 7-year period, 1947 to 1953, in 694 deaths from cancer, an over-all incidence of 18.3 per cent (127 cases) of metastases to the heart was observed. In a group of 169 cases of lymphoma, leukemia, and myeloma, there was an incidence of 36 per cent (61 cases) of metastases to the heart. In the remaining 525 cases, there was an incidence of 12.6 per cent (66 cases) of metastases to the heart. In 61 of these, gross lesions were present, an incidence of 11.6 per cent (61 cases) of gross metastases to the heart. These figures are comparable to those reported in other series.

Summario in Interlingua

Es presentate un revista del litteratura de canceres metastasiate al corde. Un nove classification es proponite.

Le protocollos autoptic del Hospital New York esseva analysate. In le curso del 7 annos ab 1947 usque a 1953, le serie total de 694 mortes ab cancere revelava un incidentia de 127 casos (i.e. 18,3 pro cento) de metastases al corde. In le subgruppo de 169 casos de lymphoma, leucemia, e myeloma, il habeva 61 metastases al corde, i.e. un incidentia de 36 pro cento. In le remanente 525 casos del serie total, 66 metastases al corde esseva notate, i.e. un incidentia de 12,6 pro cento. In 61 de iste 66 metastases, i.e. in 11,6 pro cento del del serie de 525 casos, le lesiones cardiac esseva de importantia macroscopic. Iste cifras es comparabile al cifras reportate pro altere series.

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Austin Flint

Austin Flint was born on October 20, 1812, at Petersham, Massachusetts, the fourth in a succession of a medical ancestry, his father having been a surgeon. He was educated at Amherst College and graduated at the age of 21 from the Harvard Medical School, where he had been influenced by teachers such as James Jackson, Sr., John C. Warren, and Jacob Bigelow. He praticed medicine in Boston and Northampton and later in Buffalo, and at the age of 32 was called to Chicago as Professor of Medical Theory and Practice at the Rush Medical College. He subsequently occupied many important positions including professorships at the University of Louisville, Buffalo Medical College, and New Orleans School of Medicine. In 1860 at the age of 48 he became Physician to the Bellevue Hospital in New York City and Professor of the Principles and Practice of Medicine. For 8 years he was simultaneously Professor of Pathology and Practical Medicine in the Long Island College Hospital, until overwork forced him to curtail his activities. He was a talented teacher and an ardent student of disease, addressing his efforts particularly to the refinement of the diagnostic procedures of Auenbrugger and Laennec. His numerous publications were based on voluminous, handwritten memoranda which are said to have comprised over 16,000 pages. Austin Flint is best remembered by the eponym which bears his name "The Austin Flint Murmur." This phenomenon was first noted in 1860 and described in detail in 1862 in the publication "On Cardiac Murmurs" that appeared in the *American Journal of Medical Sciences.*

Austin Flint died on March 13, 1886, at the age of 74, of cerebral apoplexy and was buried in Boston. His contemporary, Dr. Samuel D. Gross, paid the following tribute to him, "As a diagnostician in diseases of the chest he has few equals. Nor is this fact at all surprising when we bear in mind the time and the immense labor which, from an early period of his professional life, he has devoted to their investigation. I know of no one who is so well entitled as Austin Flint, Sr. to be regarded as the American Laennec."
—EDITOR.

ABSTRACTS

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ATHEROSCLEROSIS

Morris, T. G.: A Comparison of Methods for the Estimation of Serum Cholesterol and Values in Random Samples of Populations in the 55-64 Age Group. J. Clin. Path. **12**: 518 (Nov.), 1959.

Cholesterol levels in random samples of populations in different areas were measured in the age group of 55 to 64. There is a general upward trend over the years 55 to 59 and then a fall to the age of 64. Levels were higher in women than in men. Results were consistent with findings in studies by other researchers. Six methods of estimating blood cholesterol levels were compared with a standard test solution and with each other by carrying out determinations in triplicate by each method on 10 sera. Trinder's method was the most reproducible, and those of Anderson and Keys (K.5) and Sperry and Webb were the next. Sackett's method was the least reproducible. Mean levels obtained with the methods of Sperry and Webb and Anderson and Keys did not differ; the mean by Trinder's method was 4.2 per cent higher; by Sackett's method, 7.3 per cent higher; by Pearson's method, 8.8 per cent higher; and by Zlatkis' method, 51.8 per cent higher. For routine use Trinder's method is most suitable and involves less manipulation and time. Anderson's and Keys' method is also quite suitable. There are 2 major types of technic. Pearson's and Zlatkis' methods involve adding reagents directly to the serum. In the others, the cholesterol is first extracted, either by solvents or by digitonin precipitation. In all the methods, colorimetric technics are used.

MAXWELL

Schlüssel, H., Schulte, M., Heinrich, W., and Hamacher, J.: Athletics and Atherosclerosis. Ztschr. Kreislaufforsch. **48**: 734 (Aug.), 1959.

Twenty-eight guinea pigs given a dietary supplement of goose liver and cholesterol and subjected to daily exercise for 102 days showed significantly lower serum lipid and cholesterol levels and incidence of aortic atheromatosis than 28 guinea pigs given the same supplement but not exercised. The blood pressure amplitude was also lower. It is concluded that athletic activity in man has a similar preventive effect on atherosclerosis.

LEPESCHKIN

Wright, A. S., Pitt, G. A. J., and Morton, R. A.: Cholesterol Ester Fatty Acids in Atheroma and Plasma. Lancet **2**: 594 (Oct. 17), 1959.

One current hypothesis relates atherosclerosis to a deficiency in essential fatty acids and presumes that fatty acids esterified with cholesterol in atheromatous tissue will be more saturated than those esterified with cholesterol in normal plasma. Studies were performed to ascertain how much difference in saturation there might be between cholesterol esters in normal blood and in atheromatous tissues. Tissues obtained at postmortem examination were extracted and the extracts subjected to chromatography, iodine value determination and fatty acid analysis. The fatty acids esterified with cholesterol (CFA) in plasma had a higher iodine value and a lower saturated acid content than the CFA from aortas. There were no significant differences in the esters from aortic plaques and from residual aortic wall or

from coronary arteries. Studies of plasma CFA demonstrated the iodine value to be chiefly influenced by the linoleic and arachidonic acid content. There was an inverse relation between CFA iodine value and total plasma cholesterol level. Current evidence indicates that neither the extent of atherosclerosis nor the presence of coronary infarction is associated with a relative deficiency of essential fatty acids in CFA.

KURLAND

Anderson, M. N., Mendelow, M., and Alfano, F. A.: Experimental Studies of Heparin-Protamine Activity with Special Reference to Protamine Inhibition of Clotting. Surgery **46**: 1060 (Dec.), 1959.

Heparin was administered intravenously to adult healthy mongrel dogs and serial protamine titrations were carried out at hourly intervals. The level of heparin thus measured decreased by approximately 50 per cent per hour. Protamine in doses of 75 per cent or more by weight of the heparin invariably produced complete neutralization when given 15 minutes after the heparin. At longer intervals, proportionally less protamine was required to neutralize the residual active heparin. With larger doses of protamine there was an irregular, but definite incidence of protamine inhibition of clotting. There was no direct relationship between the relative amount of protamine given and the degree of inhibition of clotting. The increase in coagulation time above normal was usually small, rarely exceeding 15 minutes. There was no evidence found for a "heparin rebound," in the sense of a secondary or delayed rise in the level of active heparin. The possibility of protamine inhibition of coagulation being incorrectly interpreted as "heparin rebound" is discussed.

SHEPS

Billimoria, J. D., Drysdale, J., James, D. C. O., and Maclagen, N. F.: Determination of Fibrinolytic Activity of Whole Blood. Lancet **2**: 471 (Oct. 3), 1959.

The present paper reports a method that is rapid and reproducible for the quantitative assay of labile fibrinolytic activity of whole blood within a few hours. The rate of lysis is followed by means of hourly estimation of the hemoglobin content of the clot; 50 per cent lysis time is determined. Tests were carried out on 17 normal subjects and on 36 patients suffering from a variety of diseases including coronary occlusion, diabetes mellitus, cancer, and myxedema. Diurnal variation at least partly dependent on physical activity was demonstrated but comparatively little variation from one day to another. In most subjects, fibrinolysis times were significantly longer 2 hours after a fatty meal. There was a positive correlation between lipemia and lysis times. At 4 hours there was no significant effect. Experiments on the effect of exercise and fat feeding indicated that exercise has a considerable transient effect on accelerating fibrinolytic activity. Exercise after a fatty meal abolished the inhibiting action of fat on fibrinolysis. Studies of stypven clotting times were also made and showed shortening of clotting time after butter meals, but exercise had no effect on this finding.

KURLAND

Boyles, P. W.: Particle Size as a Factor in Thromboplastin Formation. Blood **14**: 1063 (Sept.), 1959.

Latex particles with diameters of 0.14 μ have been shown to be partially effective in the absence of platelets or phospholipids in the thromboplastin generation test. The author concludes that the function of platelets in the coagulation of blood may be due partially to their particle size and that the action of the "intact platelet" is not completely replaced by "lyophilized platelets" or purified phospholipid fractions.

KARPMAN

Chapple, R. V., and Singher, H. O.: The Present Status of the Clinical Evaluation of Fibrinolysin. Canad. M. A. J. **81**: 231 (Aug. 15), 1959.

The rationale of human fibrinolysin (plasmin) therapy is summarized, and some results obtained in over 300 patients with thromboembolic disease are described. Treatment begun early, before the clot organized (5 to 7 days), was more often efficacious. For example, 83 per cent of cases of phlebothrombosis treated within 5 days responded well, whereas 62 per cent of those treated later did so. Similar results were observed in pulmonary embolism. Doses of fibrinolysin above 50,000 units daily were found to be significantly better than smaller ones. The major side effect of treatment was fever, 29 per cent of patients having febrile responses higher than 102 F. The mechanism of fever production was uncertain, but it was short-lived. Fibrinolysin, unlike trypsin or papain, does not produce gross coagulation defects, although slight fibrinogenopenia may follow its use. The authors consider the therapeutic effectiveness of fibrinolysin to be established in phlebothrombosis, thrombophlebitis, and pulmonary embolism, and to be promising in many other types of thromboembolism.

ROGERS

Coon, W. W., and Coller, F. A.: Clinicopathologic Correlation in Thromboembolism. Surg., Gynec. & Obst. **109**: 259 (Sept.), 1959.

Review of the protocols of all autopsies done at the University of Michigan Hospital during 1945 to 1954 disclosed that pulmonary thrombotic emboli were found in 606, an incidence of 13.8 per cent, and pulmonary infarction was associated in 356. In two thirds of the 606, the embolization was significant in that it caused or contributed to the patient's death. Symptoms recorded for the latter group included by per cent dyspnea in 58, shock in 28, chest pain in 22, hemoptysis in 11; physical signs were noted in 6; and there was no sign or symptom in 27 per cent. Of the whole embolism group, 19 per cent had evidence of deep venous thrombosis in the leg. A clinical diagnosis of pulmonary embolism was made in 7.1 per cent of the entire embolism group, and in 9.3 per cent of those in whom the embolism was clinically significant. In an additional 4.1 per cent of the latter group this diagnosis was suspected. Chest roentgenograms in 60 patients were suggestive of infarction in 19. Electrocardiograms were made soon after infarction in 5 patients, and evidence of "acute cor pulmonale" was found in 4. In view of the poor ability to diagnose both pulmonary embolism and thrombotic disease of the lower half of the body, a plea is made for greater clinical awareness of these disorders and for readiness to treat or to give anticoagulants prophylactically.

ROGERS

BLOOD COAGULATION AND THROMBOEMBOLISM

Didisheim, P., Hattori, K., and Lewis, J. H.: Hematologic and Coagulation Studies in Various Animal Species. J. Lab. & Clin. Med. **53**: 866 (June), 1959.

Many remarkable findings during routine hematologic and coagulation studies on 8 mammalian and 2 avian species are described. Large thrombocytes, instead of platelets, were found in chickens and ducks. These were nucleated cells, with a high glycogen content and tendency to clump, as in mammalian platelets. Clot retraction was negligible in fowls, and differences were also negligible between clotting times in glass and silicone tubes. The blood of fowls showed also low levels of prothrombin, proconvertin, and proaccelerin, and a complete lack of plasma thromboplastin component, Hageman factor activity, and "glass factor" activity. In opossum, sheep, and cow, prothrombin and proconvertin levels were also low, but in these and all other mammals studied (rhesus monkey, dog, cat, rabbit, and raccoon), levels of proaccelerin were far higher than in human beings. Mammalian Hageman factor was generally similar to human. Antihemophilic factor levels were very high in cow and sheep plasmas. Brain tissue thromboplastin showed a definite species specificity only in the opossum, chicken, and duck. Erythrocyte sedimentation time was slow in all but the dog and cat. The importance of using homologous species systems in the study of blood coagulation mechanisms is emphasized.

MAXWELL

Ehrner, L., Garlind, T., and Linderholm, H.: Chronic Cor Pulmonale Following Thromboembolism. Acta med. scandinav. **164**: 279, 1959.

The authors report 3 patients with chronic cor pulmonale secondary to thromboembolism involving the pulmonary artery. All 3 patients were young, previously healthy men with evidence of peripheral thrombotic phenomena preceding the pulmonary emboli. Exercise tolerance was low, but the pulmonary function studies including the tests of gaseous diffusion were normal. Pulmonary blood shunting occurred as indicated by an increased venous admixture in all of the patients. Pulmonary and alveolar ventilation was increased at rest and at work. Increased vascular resistance occurred, which resulted in elevated pulmonary artery pressures and subsequent right heart strain. Both the stroke volumes and the cardiac outputs were diminished in 2 patients. The authors emphasize that the diagnosis of chronic cor pulmonale following thromboembolism of the pulmonary artery should be suspected in patients with dyspnea who have normal pulmonary function studies and no evidence of primary heart disease, and especially if there is a history of peripheral thrombosis.

KARPMAN

Fuller, J. A.: Long-term Anticoagulant Treatment. Lancet **2**: 489 (Oct. 3), 1959.

Long-term anticoagulation is being used with increasing frequency but statistics on its relative safety remains uncertain. This paper is primarily concerned with the hemorrhagic complications of phenindione therapy in 217 patients treated for periods up to 3 years. The therapeutic goal was to lengthen the 1-stage clotting time to twice that of the control, the prothrombin concentration then being 12-15 per cent. Twenty-one patients died while under treatment; in 2 fatalities anticoagulant therapy undoubtedly played a part. In

18 patients, anticoagulants were withdrawn. In 7 of these, this was done because of bleeding; in 5, because of lack of intelligence or cooperation. Of the 217 cases, 105 had 194 hemorrhagic episodes, 24 severe, 31 moderate, and 139 mild. The data suggest that 1 patient in 3 will have some sort of hemorrhagic episode during the first 3 months of treatment and that thereafter the incidence of bleeding is halved. Severe bleeding occurred in 22 patients leading to 2 and possibly 3 deaths. An unduly prolonged clotting time may be revealed by a minor bruise, but it may also herald a fatal hemorrhage. Therefore, any sign of bleeding is serious. Anticoagulant therapy is best reserved for cooperative, intelligent patients. Some hemorrhagic complications are inevitable.

KURLAND

Illingworth, R. S., and Finch, E.: Ethyl Biscoumacetate (Tromexan) in Human Milk. J. Obst. & Gynec., Brit. Emp. **66**: 487 (June), 1959.

The Tromexan level in specimens of human milk were estimated at variable intervals after the administration of Tromexan. There was no correlation between the concentration in the milk and the dosage or time of administration of Tromexan to the mother. Babies receiving breast milk showed no adverse effects, but no prothrombin-time estimations or liver-function tests were carried out on the babies. However, the small quantities of drug found in the milk would indicate that the administration of Tromexan to a lactating woman is not dangerous to the baby.

SHEPS

Kawahara, H.: Alpha-Tocopherol in Prophylaxis and Treatment of Venous Thrombosis. Surgery 46: 768 (Oct.), 1959.

An alternate case study is reported on 100 postoperative patients, half of whom received alpha-tocopherol for 2 weeks. The clotting time, prothrombin time, and prethrombotic index of Kay were determined from the preoperative period to the end of the second postoperative week. There was no significant difference in the clotting time and prothrombin time, but the prethrombic index reached a "dangerous" level in 6 cases of the treatment group as compared with 2 cases of the control group. Two of the latter patients developed thrombophlebitis. The addition of intravenous calcium gluconate to certain members of the treatment group did not produce any significant differences. A further 28 cases of venous thrombosis were treated with alpha-tocopherol. Seventeen cases were "successfully treated," 8 showed some effect, and 3 "failed" in the treatment. Acute and subacute cases were treated more effectively than were chronic cases. The criteria for these statements are not given. In 4 cases of thrombophlebitis the clearance of radioactive saline injected intramuscularly was compared before and after treatment. These patients showed a definite improvement in clearance; however, the time relationships and other clinical data are lacking. The author suggests that alpha-tocopherol can control the high blood coagulability that occurs in patients with operations and therefore can prevent the development of postoperative thrombosis.

SHEPS

Kleisch, W. F., Young, P. C., and Davis, W. D., Jr.: Dangers of Prolonged Anticoagulant Therapy in Hepatic Disease. J.A.M.A. **172**: 223 (Jan. 16), 1960.

Prolonged anticoagulant therapy after vascular accidents is a well-recognized medical practice but it entails significant risks. Contraindications to anticoagulant therapy include renal disease, hepatic disease, shock, purpura, age of more than 70 years, diabetes, severe congestive heart failure, blood dyscrasias, recent neurosurgery, peptic ulcer, catheter or Wangensteen suction, hemothorax, positive reaction to fecal examination for occult blood, and persistent hemoptysis. Difficulties may be occasioned by failure of the patient to report for frequent examination or by occurrence of intermittent complications. The authors report 1 of the latter in a man who took 50 mg. of phenindione twice daily for 4 years. He was admitted to the hospital with nausea, vomiting, jaundice, and various hemorrhagic manifestations. Apparently the patient developed an acute viral hepatitis and this potentiated the therapeutic effect of phenindione. This case re-emphasizes the dangers of anticoagulant therapy in the presence of hepatic disease and emphasizes the need for careful observation of patients receiving prolonged therapy.

KITCHELL

Kwaan, H. C., Lo., R., and McFadzean, A. J. S.: Antifibrinolytic Activity in Primary Carcinoma of the Liver. Clin. Sc. **18**: 251, 1959.

Antifibrinolytic activity was studied in patients with uncomplicated cirrhosis of the liver, in cirrhotic patients with hepatocarcinoma and in healthy volunteers. There was no difference in spontaneous fibrinolytic activity in patients with hepatocarcinoma and healthy controls but activity was significantly greater in the group with cirrhosis of the liver. Fibrinogen levels were higher in persons with hepatocarcinoma than in the con-

trol subjects, and these were higher than in the cirrhotic patients. No significant change in fibrinolytic activity followed the injection of epinephrine in patients with hepatocarcinoma, whereas significant increases were encountered in the healthy control subjects and even greater increases in the cirrhotic patients. Both control groups responded to ischemia with increased fibrinolytic activity, but none was found in the tumor group. Four patients were studied before and after the development of hepatocarcinoma. The later results showed a reduction in fibrinolytic activity to normal and elimination of the response to epinephrine and ischemia. Significantly greater antifibrinolytic activity was found in the plasma of patients with hepatocarcinoma than in the controls. A saline extract of tumor exerted greater effect than normal liver. Since no increase in antiplasmin activity was found, it was concluded that the factor responsible for these phenomena did not act directly on plasmin but inhibited the activator that converts plasminogen to plasmin.

KURLAND

Lyburn, E. F. St. J.: The Effect of Sweating on the Prothrombin Times of Blood. J. Clin. Path. **12**: 116 (Mar.), 1959.

Estimation of prothrombin times in man before and after exposure to high environmental temperatures indicates an increase in prothrombin time after sweating. The study was conducted on 2 groups of patients. One group was on anticoagulant therapy for thrombotic disease, and the other was not on anticoagulant therapy. The average rise in prothrombin times following treatment combined with anticoagulant therapy was 93 seconds, and without anticoagulants the average rise was 10 seconds. The blood failed to coagulate after sweating in 5 subjects treated without anticoagulants.

MAXWELL

Nestel, P. J.: Fibrinolytic Activity of the Blood in Intermittent Claudication. Lancet **2**: 373 (Sept. 19), 1959.

The blood fibrinolytic activity in 30 male patients with intermittent claudication as a manifestation of extensive arterial thrombosis was compared to the activity in the blood of 30 men who had no symptoms or signs of peripheral arterial disease. The fibrinolytic activity was significantly depressed in the patients with claudication. It is unknown whether this decreased activity is causally related to the disease or is a consequence of disturbed lipid metabolism.

KURLAND

Owren, P. A.: Thrombotest: A New Method for Controlling Anticoagulant Therapy. Lancet **2**: 754 (Nov. 7), 1959.

A new method has been devised for the control of anticoagulant therapy. For maximum simplicity an "all-in-one-reagent" has been devised which contains cephalin, thromboplastin and substrate-plasma with a high and constant content of all clotting factors. Calcium chloride is added in optimal concentration. Lyophilized and vacuum-sealed, the reagent is stable for 12 months. When the patient's blood or plasma is added, clotting time will depend only on the concentration of factors IX, VII, Stuart factor, and prothrombin. The high stability of the reagent makes possible the use of a standard dilution curve. The method provides good sensitivity; the therapeutic range is 10-30 per cent of normal. Sources of error lie in coagulation in capillary blood, contact activation of the test sample, inactivation of clotting factors, non-optimal calcium concentration, and the presence of heparin. The technic is simple; little equipment is needed; reliable results can be obtained with little experience.

KURLAND

Peel, A. A. F.: Thromb-elastography in Investigation of Blood Coagulation and in the Control of Anticoagulant Treatment. Scottish M. J. **4**: 422 (Sept.), 1959.

Details are given on the use of the thrombelastograph. The normal thrombelastogram is described and the variations induced with heparin in vitro and in vivo are also outlined. Following the administration of "Dindevan," there was no change in the thrombelastogram until the prothrombin time had been increased beyond twice the control value. Abnormalities are described in some cases of coronary thrombosis prior to the institution of anticoagulant therapy that suggest the presence of accelerated coagulation due to an autogenous anticoagulant with a heparin-like action. It is suggested that the thrombelastograph is a sensitive indicator of liability to either spontaneous thrombosis or hemorrhage. It suggested further that the thrombelastograph is a more sensitive indicator of hemorrhagic tendency than the prothrombin-time estimation during the administration of anticoagulants.

SHEIS

Shadid, J. N.: Venous Thromboembolism. Surgery **46**: 588 (Sept.), 1959.

The experience gained with the use of a blood-drop test on 610 patients with known or

suspected venous thromboembolism is outlined. This test consists in timing the interval taken by 14 drops of blood to fall from the tip of a standardized test instrument. This is compared to a water-drop time standard and the ratio again compared with the hematocrit level. The author suggests that certain alterations in these measurements reflect a hypercoagulable state during which thrombosis may occur if there is concomitant vascular damage. This state may be temporary and not recur or may persist for years. It is further suggested that while these alterations persist, anticoagulants should be administered. In those patients who show no alteration in the blood-drop test from normal, and have superficial venous thrombosis or suspected venous thromboembolism, anticoagulants need not be given. They are treated with symptomatic anti-inflammatory measures. When the alteration is great to begin with, or persists for longer than 2 weeks, anticoagulant therapy with heparin and oral anticoagulants is begun. Between these extremes, intramuscular heparin alone is the treatment of choice. Deep venous ligation was undertaken when patients had recurrent (3 or more) pulmonary emboli, despite adequate anticoagulant therapy. Long saphenous vein ligations were carried out on patients who had superficial venous thrombosis in varicose veins. It is concluded that the blood-drop test isolates for concentrated attention those patients requiring prolonged meticulous treatment. In addition it is said to indicate the specific need for anticoagulant therapy.

SHEPS

Steinmann, B., Imhof, P., Butler, K., and Keller, H.: On the Mode of Action of Nicotinic Acid and Its Use in Hemiplegia. Cardiologia **35**: 310, 1959.

The authors confirmed reports by others that nicotinic acid has fibrinolytic properties. They found that the intravenous injection of 1 to 2 mg. of nicotinic acid per Kg. produced in more than half of the subjects complete fibrinolysis as measured by thromboelastographs. The action was usually transient and was no longer demonstrable 1 hour after the injection. After ingestion of 1.0 Gm. of nicotinic acid, longer lasting fibrinolysis was achieved. The incidence of thromboembolic phenomena was compared in 209 patients with hemiplegia, many of whom had not received nicotinic acid for varying periods. The frequency of thromboembolism was increased 4-fold during periods when the drug was not being given. The difference was even more striking in the group of patients with atrial fibrillation. Nicotinic acid had no effect on coagulation. The drug thus offers some of the advantages of anticoagulants without any of their dangers.

BRACHFELD

CONGENITAL ANOMALIES

Bender, F., Menkhaus, B., and Portheine, H.: Unusual Systolic-Diastolic Engine Murmur in Atrial Septal Defect. Ztschr. Kreislaufforsch. **48**: 762 (Aug.), 1959.

A 28-year-old woman with atrial septal defect and moderate pulmonary hypertension showed an intense systolic murmur continuing beyond the second component of a reduplicated second heart sound, into the mitral part of diastole; the murmur had maximal intensity in the second interspace in the left midclavicular line. After operative closure of the septal defect, the murmur disappeared completely, and the terminal portion of the vectorcardiographic QRS loop became directed less to the right. The murmur, which could not be distinguished from that characteristic for patent ductus arteriosus, is attributed to increase pulmonary flow.

LEPESCHKIN

Gensini, G. G., Caldini, P., Casaccio, F., and Blount, S. G., Jr.: Persistent Left Superior Vena Cava. Am. J. Cardiol. **4**: 677 (Nov.), 1959.

The subject of persistence of the left superior vena cava was reviewed historically, embryologically, and clinically, emphasizing the authors' experience with 37 patients. The significance of this uncommon abnormality lies in its occasional interference with cardiac catheterization via the left arm, the need to occlude it during open-heart surgery and especially in its usual association with hemodynamically significant lesions, such as atrial septal defect, in 25 patients or anomalous pulmonary venous return in 15 patients. The diagnosis of persistent left superior vena cava could be strongly suspected in 86 per cent of the group by finding a significant widening of the vascular pedicle at the level of the third rib in a posteroanterior chest roentgenogram. Confirmation was obtained by angiography or by noting the course of a catheter as it passed along the vessel.

ROGERS

Ginefra, P., Costa Rocha, J., Espino Vela, J., De la Cruz, M. V., and Cisneros, F.: Clinical and Anatomic Analysis of 14 Cases of Patent Foramen Ovale Present in Various Acquired Cardiopathics. Arch. Inst. Cardiol. México **29**: 313 (May-June) 1959.

Fourteen cases of persistent foramen ovale, which were selected among 2,055 autopsy reports,

were studied. Clinical, radiologic, and electrocardiographic studies were reviewed. Six patients had rheumatic heart disease with a double mitral lesion; 3 had secondary hypertension; 1 had lupus erythematosus; 1 had syphilitic aortitis with aortic regurgitation; 2 had atherosclerotic heart disease, and the last patient had an infectious pulmonary disorder. The patients were in heart failure and 7 had unquestionable clinical signs of arterial pulmonary hypertension. Nine had variable degrees of cardiomegaly. When the pressure in the right atrium increases for any reason, the foramen ovale may theoretically open and become functional, permitting a right-to-left shunt. The authors believe that the right atrial pressure must reach very high levels before overcoming the resistance presented by the valve of the foramen ovale, as the right atrium is capable of dilating markedly before elevating its pressure. One factor that prevented the right-to-left shunt was the presence of pathologic circumstances which tended, per se, to elevate the pressure within the left atrium simultaneously. Anatomic characteristics of the adult septum also preclude shunting. The electrocardiogram did not aid in the diagnosis of the presence of a patent foramen ovale. Of the 14 patients studied, 8, due to the peculiar conformation of the foramen ovale and its valve, probably could not become functional; in 5 patients a functional foramen ovale seemed possible and only 1 case was consistent with a true functional foramen ovale. In the authors' experience a functional foramen ovale is extremely rare.

BRACHFELD

Haggenmiller, W., Engers, J., and Ell, O.: Personal Observations on 5 Cases of Cardiac Anomalies in One Family. Ztschr. Kreislaufforsch. **48**: 658 (July), 1959.

The father of the family died at the age of 27 of heart failure, and a large atrial septal defect of the ostium primum type was found at autopsy. His daughter showed an atrial septal defect leading to death at 5 months, which was confirmed at autopsy. A brother and sister who had the same grandparents and great-grandparent as the first 2 patients showed an atrial and ventricular septal defect respectively, while their cousin showed an ostium primum type of atrial septal defect. The 3 patients died at an age of less than 4 months, and the diagnosis was confirmed at autopsy. In none of the patients was the mother exposed to virus infection, roentgen radiation, or metabolic disturbances, but in 1 patient the pregnancy was preceded by 3 abortions. These patients emphasize the importance of hereditary factors in the genesis of congenital cardiac anomalies and show also that a large atrial septal defect can lead to early cardiac failure through volume overload.

LEPESCHKIN

Kenner, Th.: The Arterial Pulse in Coarctation of the Aorta. Ztschr. Kreislaufforsch. **48**: 739 (Aug.), 1959.

The typical triangular pulse configuration, which is observed in human aortic coarctation and appears also during local compression of the thoracic aorta in experimental animals, could be reproduced when an artificial pulse was sent through a rubber tube and the latter compressed in the middle. This led to decreased higher oscillatory harmonics in the central and peripheral segments of the tube, and caused both to resemble the response of a simple elastic reservoir. The pulse wave velocity remained unchanged.

LEPESCHKIN

Kerkovits, G., and Detreházy, K.: Spontaneous Delivery in Pulmonary Stenosis and Partial Heart Block. Ztschr. Kreislaufforsch. **48**: 604 (July), 1959.

A 28-year-old woman with pulmonary stenosis had 2 normal deliveries after an interval of 7 years. During the second delivery 3:2 atrioventricular block with high ventricular escape beats appeared; this could be provoked also after delivery by the erect position.

LEPESCHKIN

Maranhao, V., Raber, G. T., and Goldberg, H.: Pure Ventricular Septal Defect with Pulmonic Stenosis. Hemodynamic and Clinical Changes Following Open Heart Surgery. Am. J. Cardiol. **4**: 155 (Aug.), 1959.

The preoperative and postoperative status of 12 patients whose ventricular septal defect appeared to have been completely repaired are described. Five of these additionally had pulmonic stenosis, which was corrected simultaneously. Of the pure septal defect group, 3 were asymptomatic before and all were asymptomatic after surgery. The grade III-IV harsh systolic murmur decreased or disappeared in all except 1. The heart increased slightly in size, and complete right bundle-branch block appeared in all patients. Four had moderate pulmonary hypertension which returned to normal after surgery. Of the septal defect plus pulmonic stenosis group, all were symptomatic preoperatively, and 1 was cyanotic. The uniformly present grade I to IV left sternal border systolic murmur persisted but in lesser intensity postoperatively. Again, the heart size increased slightly and complete right bundle-branch block developed in all patients.

The moderately elevated ventricular pressure fell postoperatively in each instance, and in 3 it reached normal levels. Open-heart surgery when indicated was considered to be the treatment of choice for ventricular septal defect, with or without pulmonic stenosis.

ROGERS

Rudolph, W., Bernsmeier, A., and Blomer, H.: The Diagnosis of Atrial Septal Defect from Phonocardiographic and Auscultatory Findings. Arch. Kreislaufforsch. **31**: 112 (Oct.), 1959.

The heart sounds in 30 patients with confirmed atrial septal defect (ostium secundum defect with left-to-right shunt) were examined phonocardiographically and by auscultation. The recording was performed simultaneously with 2 microphones at various sites of auscultation during breath holding, normal respiration, and cardiac catheterization. Simultaneous tracings were recorded of the electrocardiogram, respiration, pressure pulses from various cardiac chambers as well as carotid pulse curves. The first sound was split in 17 patients. An early systolic ejection click was noted in 2 patients, which was correlated with a marked widening of the pulmonary artery. In all patients, a spindle-shaped systolic ejection murmur was heard over the pulmonic area, with a maximum prior to midsystole and ending always before the aortic component of the second sound (relative pulmonary stenosis). The interval between the 2 components of the second sound (which was split in all patients) remained practically constant during respiration. In 2 patients, an early-diastolic, high-pitched, decrescendo murmur occurred over the pulmonary area as an expression of relative pulmonary insufficiency. A middiastolic murmur was heard in 19 patients. A presystolic murmur was noted in 9 patients. In 6 patients the rapid pulse rate did not permit differentiation between a middiastolic and presystolic murmurs or summation of these 2. In 6 patients, both murmurs could be demonstrated separately. On the basis of these findings it appeared possible to diagnose an atrial septal defect by means of phonocardiogram and auscultation. The combination of a systolic murmur over the pulmonary area, fixed splitting of the second sound, and a middiastolic murmur characterized an atrial septal defect.

BRACHFELD

CONGESTIVE HEART FAILURE

Buckley, N. M., and Zeig, N. J.: Acute Unilateral Ventricular Failure in the Isolated Dog Heart. Am. J. Physiol. **197**: 247 (July), 1959.

Acute left ventricular failure was studied in the isolated dog heart exposed to elevated aortic resistance. Experiments in which only the left ventricle performed mechanical work showed that progressive changes in distensibility and contractility occurred. When exposure to the elevated resistance was prolonged, the failure became hemodynamically irreversible and there was a loss of responsiveness to increases in filling pressure. Experiments in which both ventricles worked under separately controllable hemodynamic conditions established that acute failure did not develop in the adjacent right ventricle. The observations suggest that the unilateral ventricular failure involved a permanent alteration of the distensibility and contractility of the wall of the left ventricle as a result of a process that permitted the right ventricle to retain normal function.

KAYDEN

Rachmilewitz, M., Stein, Y., Aronovitch, M.Sc., and Grossowicz, N.: Congestive Heart Failure. Arch. Int. Med. **104**: 405 (Sept.), 1959.

Liver-cell damage is associated with markedly increased levels of cyanocobalamin (vitamin B_{12}) in the blood due to the release of this vitamin from damaged hepatic cells. This report deals with observations on cyanocobalamin activity in the serum of patients with congestive heart failure and hepatomegaly. This vitamin was increased in 23 of 28 patients suffering from severe chronic congestive heart failure. In these patients the commonly used tests for hepatocellular function were usually normal. As the congestive heart failure was controlled, the levels of serum cyanocobalamin decreased considerably. The authors relate the increased release of this vitamin into the serum to anatomic changes in the hepatic architecture. These consist of centrilobar necrosis, resulting from hepatic anoxia and hemorrhages from the distended sinusoids due to the increase in venous pressure. The highest levels of serum vitamin B_{12} were found in patients with long-standing heart failure.

KRAUSE

Wener, J., Friedman, R., Mayman, A., and Schucher, R.: Hydrochlorothiazide (Hydrodiuril) in the Management of Cardiac Edema. Canad. M. A. J. **81**: 211 (Aug. 15), 1959.

The action of hydrochlorothiazide was observed during periods up to 3 months in 4 hospitalized and 27 ambulatory patients with congestive failure due to acquired heart disease. All patients were previously under treatment including chlorothiazide, digitalis, and sodium chloride restriction to 4 to 6 Gm. daily. Therapeutic dosage was usually 50 to 100 mg. twice daily, the effectiveness of which was equal to that of 1 to 2 ml.

of meralluride. Thirteen patients responded further to hydrochlorothiazide in terms of weight reduction of 4 to 8 pounds. Several ceased to require mercurial diuretics. The diuretic response was prompt and included a nearly parallel increase in sodium and chloride output with lesser increases in elimination of magnesium and potassium. Few serum electrolyte imbalances were encountered, and only 1 instance of hypokalemia was noted. Side effects of therapy included dryness of the mouth, paresthesia of the face and hands, and gastrointestinal disturbances; but all were mild, and none required discontinuance of the drug. It was concluded that hydrochlorothiazide was more potent than chlorothiazide and caused fewer serum electrolyte disturbances.

ROGERS

White, K. L., Martin, D. A., and Vernon, C. R.: Venous Pressure, Emotions, and Congestive Heart Failure. J. Chron. Dis. **10**: 163 (Sept.), 1959.

Little is known about the physiologic, psychologic, and environmental circumstances associated with the initiation of congestive heart failure. In many patients precipitating factors are difficult to demonstrate. The literature dealing with the influence of emotional factors on certain aspects of cardiovascular function is reviewed briefly. In an attempt to understand better the frequently unexplained onset of congestive heart failure, a series of studies was designed to examine the effects of emotional stimuli on central venous pressure and peripheral venous tone, and to evaluate the significance of specific emotional experiences in relation to the symptoms of congestive heart failure. Central venous pressure (CVP) was measured by means of a catheter advanced to the central veins. Peripheral venous segment pressure (PVSP) was measured with the catheter tip in the forearm vein. CVP increased in response to physical stimuli, as lifting a 2 Kg. weight, to "neutral" and "stressful" rhetorical questions, and to repeated emotional stimuli in 25 studies of 22 patients, and to psychiatric interviews of 10 patients. The data justify these conclusions: experiences which a patient with heart disease considers emotionally "stressful" can be elicited and predicted with a fair degree of confidence during a short medical interview; in varying degrees of congestive failure, rhetorical questions, which a patient considers intellectually and emotionally, are associated with varying but definite CVP increases of as much as 45 cm. of water. Psychiatric studies of patients may explain poor responses in spite of superior medical regimens. PVSP in 6 healthy subjects was modified by emotional stimuli, and was of greater magnitude and duration than seen with physical stimuli. Disturbing life situations and the emotional reactions evoked may cause recurrent and cumulative increases in peripheral and central venous pressure.

MAXWELL

CORONARY ARTERY DISEASE

Alexander, W. D., Macdougall, A. I., Oliver, M. F., and Boyd, G. S.: The Effect of Salicylate on the Serum Lipids and Lipoproteins in Coronary Artery Disease Clin. Sc. **18**: 195, 1959.

Aspirin was administered for 8 weeks to 5 men and 4 postmenopausal women with hypercholesteremia and angina pectoris in doses of 5 to 8 Gm. daily, yielding a serum salicylate level of about 40 mg./100 ml. The serum cholesterol was consistently reduced after 2 weeks of treatment. Although basal metabolism was increased, there was no increase in angina on effort nor any change in the electrocardiogram. A second study was made after administration of 3.3 Gm. and 5.0 Gm. of aspirin daily to 6 hypercholesteremic men and of 4 and 8 Gm. daily to 6 postmenopausal women. Doses less than 4 Gm. daily were ineffective. The group with the highest serum salicylate concentration showed the greatest decrease in serum cholesterol but the effect may not be directly related to an increase in metabolic rate.

KURLAND

Baronofsky, I. V., Senderoff, E., Welberry, A. D., and Kaneko, M.: Experience with Attempts at Ventricular Defibrillation in the Presence of Acute Coronary Occlusion. Ann. Surg. **151**: 193 (Feb.), 1960.

Ventricular fibrillation is responsible for a great percentage of deaths following acute myocardial infarction. There have been successful attempts at defibrillation reported but acceptance has been slow because of technics involved and the feeling that successful defibrillation is rare unless the occlusion is first removed. The authors have reported here on their method of defibrillation in a series of 25 dogs in which myocardial infarction was produced experimentally by ligation of the anterior descending branch of the left coronary artery. Twenty-two of the 25 animals developed ventricular fibrillation within 2 to 25 minutes following ligation. Eighteen of the 22 dogs were successfully defibrillated. The method used was one of electrical countershock into the fibrillating ventricles of 1.5 to 3.0 amperes, with a duration of 0.15 second and an amplitude of 150 volts. The pulses can be given as often as 1 per second. Three rapid shocks were given. If this was effective in restoring a beat then 100 mg. of pronestyl and 0.5 mg. of

ouabain were given by intracardiac injection. The ligatures were left intact. If electrical countershock was ineffective after several attempts, pronestyl was injected and countershock attempted. With the return of an effective beat, ouabain was then given. In instances of refibrillation, electric defibrillation and massage were utilized. In those instances in which response was not obtained with the above measures, epinephrine and calcium were also utilized. All the animals that survived 10 hours to 60 days required only countershock, 100 mg. of pronestyl, and 0.5 mg. of ouabain for successful resuscitation. In all but 3 of these countershock alone was effective. No dog that required more than the above measures survived more than 3 hours in spite of increased ouabain, calcium, and epinephrine. Following ligation a large cyanotic area of infarction developed in an area corresponding to distribution of the ligated vessel. This persisted in spite of return to an adequate beat. Immediately following ligation there was marked decrease in the peripheral coronary artery pressure and reduction in coronary backflow. In those animals surviving 60 days these values increased and with barium injection studies anastomotic channels were demonstrated. With this experiment and an analysis of the human cases of successful defibrillation reported it would appear that countershock would be the most effective weapon probably best applied through the open chest. Multiple countershocks appear to be necessary. Pronestyl is successful in combating multiple premature ventricular contractions and fibrillation. In these animals ouabain seemed to increase the effectiveness of cardiac contractions.

LEVINSON

Cohen, G., Dardick, I., and Greenblatt, J.: Pleurisy and Pericarditis Complicating Myocardial Infarction. The So-Called Post Myocardial Infarction Syndrome. Canad. M.A.J. **82**: 123 (Jan. 16), 1960.

Ten case reports of this unusual syndrome were presented. Each followed typical acute myocardial infarction by periods ranging from several hours to 3 weeks. The syndrome was characterized by evidences of pleurisy with or without effusion in all patients and by pericarditis in at least 9 with pericardial effusion in 3 or more of these. Pneumonitis was found in 2 instances, and cardiac tamponade was not observed. There was moderate but variable fever. Aside from electrocardiographic changes suggesting pericarditis (in 3 patients) and roentgenographic findings, laboratory data were of help only in a negative sense. Both the clinical picture and course were variable, the duration ranging up to 3 months. Recurrences were observed in 5 patients. In these and in previously described examples the disorder has been benign and its importance lay chiefly in distinguishing it from new myocardial infarction, pulmonary infarction, or sepsis. Treatment was symptomatic, although corticosteroid therapy was employed in 2 patients, both with dramatic effect. Anticoagulant therapy generally was considered to be contraindicated during pericarditis. The pathogenesis remained speculative; viral infection and hypersensitivity were thought possibly to be involved.

ROGERS

Gillot, P.: Therapeutic Value of L. 2329 in Angina Pectoris. Acta cardiol. **14**: 494, 1959.

One hundred and eighty patients with angina pectoris, without associated hypertension or valvular lesions, were treated with L. 2329 (a benzofuran derivative) for periods varying from 7 months to 2 years. The daily doses varied from 75 mg. to 450 mg.; 300 mg. had a therapeutic result in most cases. In 77 per cent of cases, a good or excellent effect was observed, manifest by a substantial reduction in the number of painful attacks after effort or at rest, or in their total disappearance. In many cases, an objective improvement in the electrocardiographic tracing was observed; this normalization occurred immediately when L. 2329 was given intravenously but more slowly after rectal or oral administration. No side effects on heart rate or blood pressure or thyroid function or on the blood components were observed. Toxic phenomena were never seen, even after the intravenous administration of large doses (450 mg). Slight gastric intolerance occurred in 2 per cent of patients, after oral doses only. The onset of action of L. 2329 by mouth was much slower but of much longer duration than that of nitroglycerin.

BRACHFELD

Kamil, M., and Klinger, I.: Time-Disintegration Capsules of Pentaerythritol Tetranitrate in Selected Anginal Group. New York State J. Med. **59**: 3398 (Sept. 15), 1959.

Nitroglycerin is the best medication to relieve the anginal distress of coronary insufficiency. Its chief disadvantage is its short duration of action, which limits its value as a prophylactic agent against anginal pain. For long-acting use the best drug seems to be pentaerythritol tetranitrate, and the authors tested the value of this chemical agent in timed-disintegration capsules. Twenty patients with coronary artery

insufficiency and angina pectoris showed an excellent improvement by the reduction of from 50 to 85 per cent in nitroglycerin requirements when treated with 2 such capsules daily 12 hours apart using a double-blind technic for 1 year. Using the single-blind technic 17 out of 20 patients showed an excellent response. Oscillometric readings were improved 62 per cent in double-blind study groups and 56 per cent in the single-blind group. The ability to walk greater distances was prominent in both groups. Twenty patients treated for 12 months on placebos were dissatisfied and unimproved until they were placed on the continuous release medication. This form of pentaerythritol tetranitrate has been shown to be remarkably more efficient for relieving angina for long periods of time than any other comparable medication.

KRAUSE

Kauntze, R., McGill, D., and Brock, R.: The Surgical Relief of Chronic Myocardial Ischaemia. Lancet **2**: 631 (Oct. 24), 1959.

Many surgical procedures have been devised in an attempt to increase the blood supply to the ischemic myocardium by the development of a collateral circulation. There is no evidence that any of these operations are effective in bringing a new blood supply to the heart. However, a simple procedure was adopted of abrading the parietal and visceral pericardium to produce a myocardial reaction sufficiently brisk to improve the intercoronary anastomoses. Occasionally, internal mammary ligation was included. The indication for operation was progressive and incapacitating angina without cardiac enlargement or cardiac failure unresponsive to medical therapy. Preoperative assessment included clinical and laboratory evaluation and a standard exercise test under stable conditions. Ten patients are described with 1 death. The results were striking in 3 cases, good in 5 and slight in 1. Abrasion of the pericardium produces the electrocardiographic appearance of lateral wall infarction. Hence, postoperative assessment was mainly clinical. While the psychologic impact must be considerable, improvement in pain and effort dyspnea was greatest after 4 months when such effects might be expected to be waning.

KURLAND

Laurie, W.. Woods, J. D., and Roach, G.: Coronary Heart Disease in the South African Bantu. Am. J. Cardiol. **5**: 48 (Jan.), 1960.

All 206 adult patients with cardiac symptoms admitted to the Edendale Hospital in Natal during a 6-month period were included in a clinical study, which was complemented by analysis of a 12-month autopsy series of 243 patients aged 35 years and over. The presence of ischemic heart disease was suspected clinically in 3 patients with possible myocardial infarction, 8 with angina pectoris alone, and in 20 with angina plus congestive heart failure of undetermined cause. Anatomically, the coronary arteries appeared normal in 53 per cent of autopsies; 40 per cent showed slight arteriosclerosis, while severe stenosis or occlusion of 1 or more main coronary arteries was found in 7 per cent. Myocardial fibrosis was observed to a slight degree in 25 per cent, to a severe degree in 10 per cent and as a frank infarct in 1.7 per cent. It is suggested that the South African Bantu has no immunity to coronary atherosclerosis or to resultant heart disease but that he differs from Europeans who more commonly present with acute myocardial infarction. Instead, the Bantu tends to develop smaller myocardial scars with resultant "cryptogenic" heart failure.

ROGERS

Litvak, J., and Vineberg, A.: Experimental Gradual Arterial Occlusions with In Vitro and In Vivo Observations. Surgery **46**: 953 (Nov.), 1959.

The development of a satisfactory technic for the production of gradual arterial occlusion is described. The final technic involved the use of a casein plastic sleeve encased in stainless steel. These produced gradual occlusion of arteries over reasonably predictable periods of time. This occlusion resulted from reduction in external vessel diameter due to luminal swelling of the plastic, fibroplastic response of the arterial walls at the site of the sleeve, and the development of intraluminal thrombi arising concentrically from the intima. If the occlusion was complete, there was a narrow zone of thrombotic material proximal and distal to the sleeve site. There was no evidence of embolization. These sleeves produced progressive myocardial ischemia and infarction in 12 dogs without complete anatomic occlusion of coronary arteries. The dogs died from 4 to 26 days after thoracotomy. In none of the animals studied were the arterial lumina completely occluded.

SHEPS

Mandelbaum, R. A., and Brackup, A. H.: Myocardial Infarction during Gastrointestinal Hemorrhage. New York State J. Med. **59**: 2806 (Aug. 1), 1959.

Cardiac involvement in extensive gastrointestinal bleeding is due to shock and acute anemia. The hypotension causes a decrease in coronary

blood flow and the anemia in itself interferes with myocardial metabolism. Therefore, treatment consists of pressor amines in sufficient amounts to maintain the blood pressure and the use of blood transfusions in amounts equal to blood loss. In order to prevent myocardial damage, treatment should be prompt. Two case reports are presented.

KRAUSE

Marmorston, J., Moore, F. J., Magidson, O., Kuzma, O., and Lewis, J. J.: Effects of Long-Term Estrogen Therapy on Serum Cholesterol and Phospholipids in Men with Myocardial Infarction. Ann. Int. Med. 51: 972 (Nov.), 1959.

A group of 106 men with documented myocardial infarction were studied for a period of 3 to 20 months at an outpatient cardiac clinic. The patients were divided into 4 groups: 1 group was given no medication and 3 groups received oral synthetic estrogen therapy. The drugs were ethinyl estradiol, conjugated equine estrogens (Premarin) and SC6924 (Manvene), and were administered to the maximum tolerated dose for each patient. In four fifths of the patients feminization effects were noted, and in the remaining one fifth treatment had been given for only a short period of time. After 90 days of therapy the effects of estrogen on the serum lipids appeared to be maximal, and tended neither to increase nor decrease thereafter. The effects of the 3 estrogens appeared to be similar. Under estrogen therapy, initially high levels of serum cholesterol and the cholesterol to phospholipid ratio tended to fall, while initially low levels tended to remain unchanged or to rise. Untreated control patients showed little variation in their serum cholesterol levels. The changes in serum phospholipid levels in the treated group were qualitatively similar to the changes in serum cholesterol levels, but the phospholipid levels of the control group also showed changes, high values falling and low levels rising. The differences between the treated and untreated groups were not statistically significant. The effects upon serum lipids of men receiving estrogen are similar to those previously reported for estrogen therapy in postmenopausal women.

KAYDEN

Oliver, M. F., and Boyd, G. S.: Effect of Bilateral Ovariectomy on Coronary-artery Disease and Serum-lipid Levels. Lancet 2: 690 (Oct. 31), 1959.

A striking sex difference in the incidence of angina pectoris has long been recognized. A study was undertaken to determine whether a premature menopause was followed by a significant change in the incidence of coronary artery disease and in cholesterol levels. Since the peak incidence of coronary disease in women is about 15 years after the menopause, it was decided to investigate women who had had surgical removal of both ovaries, 20 or more years previously. These were compared to a group who had undergone only unilateral oophorectomy. Information was also sought about the incidence of coronary artery disease in a healthy population from a general practice in Edinburgh. During the 20 years since operation, features of coronary disease developed in 9 of 36 women who had bilateral operation and in 1 of 31 who had had unilateral ovariectomy. One woman in the bilateral ovariectomy group died from myocardial infarction before the study. There was no difference in the prevalence of diastolic hypertension or obesity between the groups. There was a significant elevation of serum cholesterol and the phospholipid ratio in the bilateral group compared to the unilateral group. Among the women with bilaterally oophorectomy, the serum lipids of those with coronary artery disease were not different from those without coronary disease. The findings indicate that clinical coronary artery disease and elevated serum cholesterol are more common in women who have had both ovaries removed prematurely than in those who have had only 1 ovary removed. It is suggested that where possible, complete removal of both ovaries be avoided and, if unavoidable, replacement therapy should be administered to the age of 50.

KURLAND

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N.Y.
Telephone Gramercy 7-9170

AHA Scientific Sessions Program

The AHA Committee on Scientific Sessions Program has selected 120 original scientific papers from a total of 392 submitted for consideration to be presented at the American Heart Association's 33rd annual Scientific Sessions. The sessions will be held from Friday, October 21 through Sunday, October 23 at Kiel Auditorium, St. Louis. These presentations will be made at Scientific Sessions under sponsorship of the Association's Councils and during six simultaneous sessions of broad clinical interest.

Registrants holding confirmed hotel reservations prior to September 30 will be mailed a copy of the full program and abstracts of papers prior to the meeting. These will also be published as a supplement to the October issue of *Circulation.*

Highlights of the Scientific Sessions program are:

Friday, October 21:

Lewis A. Conner Memorial Lecture, "Physiology of the Circulation as Viewed by the Internist" by Eugene A. Stead, Jr., M. D., Professor and Chairman of Medicine, Duke University School of Medicine; joint program of AHA Council on Clinical Cardiology and American College of Cardiology; symposium on "Atrial Arrhythmias"; concurrent sessions on arteriosclerosis, rheumatic fever and congenital heart disease, and circulation; and a session for dentists.

On Friday evening, "Fireside Conferences" are scheduled under joint sponsorship with the American College of Cardiology. These will be held at the Sheraton-Jefferson Hotel.

Saturday, October 22:

Symposium on "Problems in the Diagnosis and Treatment of Curable Hypertension"; session on "Biophysical Methods in the Study of Circulation"; George E. Brown Memorial Lecture, "Clinical Physiology of the Splanchnic Circulation," by Stanley E. Bradley, M.D., Professor of Medicine and Chairman of the Department, Columbia University College of Physicians and Surgeons; symposium on "Ventricular Septal Defects"; and morning and afternoon sessions for nurses.

Sunday, October 23:

Symposia on "Complete Heart Block," "Nondietary Factors in Coronary Artery Disease"; and "Lipids and Arteriosclerosis"; panel on "Surgery for Extracranial Occlusive Cerebrovascular Disease." There will be morning and afternoon sessions on cardiovascular films, each to be introduced and discussed by the author or other authority on the subject.

As in previous years, scientific and industrial exhibits will be on display in the Auditorium.

Registration and accommodation forms may be obtained from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

AHA Annual Assembly Meeting

The 35th Annual Meeting of the Assembly, delegate body of the American Heart Association, begins on Monday, October 24, and continues through Tuesday, October 25 in St. Louis' Sheraton-Jefferson Hotel.

Assembly delegates are invited to attend an

open press conference on Sunday afternoon on the subject of heart attacks. The Conference, under sponsorship of the Council on Community Service and Education, will be moderated by Irvine H. Page, M. D., Director, Research Division, Cleveland Clinic Foundation, and former AHA President.

The opening general session on Monday morning will hear a report on recent achievements in medical and biological research presented by James V. Warren, M. D., Professor of Medicine and Chairman, Department of Internal Medicine, University of Texas Medical Branch, Galveston.

Seven Assembly Panels will meet all day Monday to discuss the Association's programs and policies. The general Assembly convenes on Tuesday morning to discuss Panel recommendations and elect AHA officers and Board members.

The Association's Annual Dinner will be held in the Sheraton-Jefferson Hotel on Sunday evening.

AHA Grant-In-Aid Applications Deadline is November 1

Applications for Heart Association grants-in-aid for the fiscal year beginning July 1, 1961 must be received by the Assistant Medical Director for Research at the AHA National Office, 44 East 23rd Street, New York 10, N. Y., not later than November 1, 1960. The deadline for submitting applications for Research Fellowships and Established Investigatorships was September 15.

All applications must be submitted on forms obtainable from the Association. Grants are made to non-profit institutions in direct support of a particular investigator for a specific program of research under his direction. Awards are in support of research in the cardiovascular field or basic sciences for periods up to five years.

Affiliates Contribute $81,000 To Supplement National Research

The Iowa Heart Association has contributed $34,000 to supplement the AHA national research program. This brings to $81,304 the total contributed by Heart Associations over amounts regularly assigned toward the support of research in fiscal 1960-61 which the AHA Research Committee approved, but which could not be financed for lack of funds.

The Iowa contribution is in full support of grants to Drs. John W. Eckstein and Francois M. Abboud, State University of Iowa College of Medicine; Lyle H. Hamilton, Marquette University School of Medicine; Peter V. Moulder, University of Chicago School of Medicine; Laurence O. Pilgeram, St. Barnabas Hospital, Minneapolis; and in partial support of the grant to Colin H. Walker, University of Colorado Medical Center.

In addition to those previously announced, funds have been received from Heart Associations through July 15, 1960 as follows:

Illinois, $18,200, full support, Established Investigatorships, Dr. Ruth Pick, Michael Reese Hospital, Dr. Victor Pollak, University of Illinois College of Medicine; Napa Valley (Cal.), $1000, partial support, grant, Dr. Richard J. Havel, University of California Medical Center; Northwestern Ohio, $1001, partial support, grant, Dr. Ancel Keys, University of Minnesota School of Public Health; Orange County (N.Y.), $5500, full support, grant, Dr. Alan J. Johnson, New York University-Bellevue Medical Center; Roanoke Valley (Va.), $2000, partial support, fellowship, Dr. Ruben G. Lancestremere, Medical College of Virginia; and Stamford-Darien-New Haven (Conn.), $9603, full support, grant, Dr. Allen V. N. Goodyer, Yale University School of Medicine.

Lay Film on Congestive Failure Available for Use by Physicians

A new film, "Congestive Heart Failure," which may be used by physicians as a visual aid when addressing lay and paramedical groups, is available from local Heart Associations or from the American Heart Association.

Last in the series of eight films on the cardiovascular system and its diseases for lay audiences, it shows by means of animation the nature and treatment of congestive heart failure. A 16mm. color film which runs 8½-minutes, it was produced for the Association and its affiliates by Churchill-Wexler Film Productions.

Previous films in the series available to physicians are on the following subjects: circulation, congenital heart defects, coronary heart disease, hypertension, rheumatic heart disease, strokes and varicose veins.

Reference Book Available On Heart Disease Dietary Aspects

A new booklet of selected references on "Dietary Aspects of Cardiovascular Diseases" has been compiled by the U.S. Department of Health, Education and Welfare for use by professional health personnel. It is available to physicians at no cost from the Heart Disease Control Program, U.S. Public Health Service, Washington 25, D.C.

Meetings Calendar

September 26-30: Intersociety Committee on Pathology Information, Chicago. Lura Jackson, 1785 Massachusetts Ave., Washington 6, D. C.

September 27-30: American Roentgen Ray Society, Atlantic City. Hugh Jones, 20 N. Wacker Drive, Chicago 6, Ill.

October 10-14: American College of Surgeons, Clinical Congress, San Francisco. W. E. Adams, 40 E. Erie St., Chicago 11, Ill.

October 21-23: American College of Cardiology, 9th Interim Meeting, St. Louis. Philip Reichert, American College of Cardiology, 350 Fifth Avenue, New York, N. Y.

October 21-25: American Heart Association, Annual Meeting and Scientific Sessions (October 21-23), St. Louis. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

October 31-November 2: Association of American Medical Colleges, Hollywood Beach, Fla. Ward Darley, 2530 Ridge Ave., Evanston, Ill.

October 30-November 4: American Public Health Association, San Francisco. B. F. Mattison, 1790 Broadway, New York 19, N. Y.

November 3-4: International Conference "Muscle as a Tissue," Philadelphia. K. Rodahl, Lankenau Hospital, Philadelphia 31, Pa.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Mich.

November 28-December 2: American Medical Association, Clinical Meeting, Washington, D. C. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

November 30-December 3: Canadian Heart Association and National Heart Foundation of Canada, Toronto. J. B. Armstrong, 501 Yonge Street, Toronto 5, Canada.

1961

February 8-11: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill.

March 20-24: American Surgical Association, Boca Raton, Fla. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

Abroad

September 18-25: European Congress of Cardiology, Rome. V. Puddu, Clinica Medica, University of Rome, Italy.

October 19-23: Symposium on Rheumatic Diseases, Ixtapan, Mexico. General Tours, Inc., 595 Madison Ave., New York 22, N. Y.

1962

October: Fourth World Congress on Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc, 300, Mexico, D. F.

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Riker Northridge, California

Circulation

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